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INTERNAL MEDICINE REVIEW
CORE CURRICULUM

BOOK **2**

PULMONARY MEDICINE



NEPHROLOGY



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INTERNAL MEDICINE REVIEW

CORE CURRICULUM

15th EDITION

Book 2 of 5

Topics in this volume:

Pulmonary Medicine

Nephrology

Robert A. Hannaman, MD
with Candace L. Walkley, MD and J. Thomas Cross, Jr., MD, MPH, FACP

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I N T E R N A L M E D I C I N E R E V I E W



CORE CURRICULUM

15th EDITION

Robert A. Hannaman, MD
with Candace L. Walkley, MD

PULMONARY MEDICINE

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Pulmonary Medicine

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DIAGNOSTIC TESTS

CT

You need to understand a little about types of CT scans to order the proper tests, so let's dive into CT scans as they relate to pulmonary parenchymal and vascular diseases. These are pretty complicated in their techniques, but you don't need to understand much about how they work. Focus on knowing the limitations/benefits of the different types, and which to order when.

There are basically 4 types of CT scans; and within the helical CT type, there are 2 subtypes:

- 1) "Conventional" CT (cCT)
- 2) High-Resolution CT (HRCT)
- 3) Helical CT (hCT):
 - Single-section CT
 - Multidetector CT (MDCT)
- 4) Electron Beam CT

cCT ("Step & Shoot") works by shooting x-rays in an incremental axial or helical rotation. cCT scans require cables to wind and unwind, so they're slow and have a few subsequent disadvantages (e.g., respiratory misregistration and unreliable imaging of vascular structures due to timing issues). cCT is still used to look at anatomy but is not used much to evaluate lungs.

HRCT is similar to cCT, but the x-rays are thinly collimated (restricting the beam to a given area), so we can see the lung parenchyma at high resolution (down to about 5 acini surrounded by interlobular septa). HRCT is used when disease is suspected by history and physical exam, but the chest x-ray is normal or slightly abnormal (interstitial lung diseases [ILD], emphysema from α_1 -antitrypsin deficiency, bronchiectasis, lymphangitic spread of malignancy). Certain patterns and distributions of CT abnormalities are associated with histopathology in ILD, so sometimes a diagnosis can be made using HRCT without a lung biopsy. HRCT is always the first place to start when you suspect **ILD** or **bronchiectasis**! HRCT is sometimes used for focal diseases (solitary pulmonary nodules or pulmonary-renal vasculitides) to guide biopsies. HRCT does not require contrast because the lung inherently has significant contrast (soft tissue, air, etc.) and the technique of HRCT is not typically used to evaluate vasculature.

hCT (helical CT; previously called "spiral" or "volumetric") works by shooting x-rays in a continuous helical rotation using slip rings instead of cables (no need for all that winding and unwinding, and scans much faster). The first kind of hCT was called "single-section." Be aware that unless a contraindication exists, **IV contrast dye** is used with hCT.

Single-section hCT is being replaced by multidetector (or "multislice") hCT. **MDCT** is now the best method for performing CT-pulmonary angiography (CTPA)

because it sees subsegmental emboli better than single-section. MDCT is also replacing single HRCT at some hospitals because MDCT inherently provides higher-resolution images of the pulmonary parenchyma.

hCT/MDCT has these 3 distinct advantages:

- 1) Scanning large sections on a single breath (such as the pelvis and the lungs)
- 2) Collecting images precisely when the flow of contrast is in the system you're concerned about (i.e., specific blood vessels)
- 3) Narrowing of the collimation through the chest so the lung and hilar images are "high resolution"

Electron beam CT (or ultrafast CT) was initially developed for imaging of the heart. It is very fast because the x-ray source is swept electronically rather than mechanically. It is able to take multiple images within the time frame of a single heart beat and, therefore, is capable of evaluating congenital defects and pulmonary vasculature. It also gives a lower radiation dose than hCT. Electron beam CT units are rare and cost double that of an hCT unit.

Following are some CT buzzwords taken from the above items:

- Diagnose ILD or bronchiectasis = HRCT.
- Work up solitary pulmonary nodule = hCT or HRCT.
- Diagnose pulmonary embolism = CTPA (CT-pulmonary angiography) which can be done by hCT or MDCT. (In testing situations, your correct choice may be only "CTPA" or "hCT" or "MDCT" as the option.) Do not select "HRCT" to diagnose a PE!

Again, when most hospitals have added MDCT technology, we'll use it for everything in the lungs and you won't need to differentiate HRCT from MDCT anymore. You may order a "CTPA" or a "chest CT," and the test will be performed with MDCT. But for now, some hospitals and testing situations may still ask you to request "high-resolution" imaging for certain disease states and "helical CT" to diagnose pulmonary emboli.

MRI

MRI is useful only in specific situations while evaluating pulmonary disease:

- When evaluating tumors near adjacent blood vessels or nerves.
- For determining what is tumor and what is not; e.g., superior sulcus tumors, brachial plexus tumors, mediastinal tumors, tumors near the aorta or heart.
- MRI is also used at very few centers to evaluate venous thrombosis using magnetic resonance angiography (MRA) and magnetic resonance venography (MRV).

Again, HRCT and hCT are the best tools for assessing lung parenchyma and vessels.

BIOPSY

Lung biopsy is used to assist in diagnosing interstitial lung disease in patients with **atypical** clinical features and **non-diagnostic** HRCT. Biopsy is definitely performed when you need to exclude neoplastic and infectious causes of an interstitial pattern.

You can collect biopsies by the transbronchial approach, the open lung approach, or by video-assisted thoracoscopic lung surgery (VATS). The technique chosen depends on where abnormalities are located—with chest x-ray and HRCT results used to plan strategy; e.g., in sarcoidosis, transbronchial biopsy yield is highest when infiltrates are obvious on the chest x-ray (90%) and lowest (70%) when hilar adenopathy is the only abnormality.

Lung biopsy is performed if you are entertaining the diagnosis of 1 of the following: interstitial lung disease, lymphangitic spread of cancer, eosinophilic pneumonia, vasculitis, or certain infections.

As with other ILDs, lung biopsy is no longer used in evaluating possible IPF (**except** in atypical cases) because HRCT usually is diagnostic.

OTHER PULMONARY TESTS

Bronchoalveolar lavage (BAL) is an important pulmonary diagnostic tool. Know [Table 3-1](#).

Pulmonary angiogram is still considered the gold standard for pulmonary embolism diagnosis, but this test is **rarely required** anymore because CTPA is very reliable.

PET scan is useful in differentiating benign vs. malignant pulmonary nodules and infectious or inflammatory conditions (most useful with > 1–2-cm nodules).

Thoracentesis, V/Q scan, and pulmonary function tests (PFTs) are covered in their respective sections.

RESPIRATORY PHYSIOLOGY

Acid-Base is covered in depth in the Nephrology section, Book 2.

Know respiratory physiology well. The information pops up repeatedly on the Boards.

SHORT REVIEW

Atmospheric pressure (P_b): The pressure of the atmosphere varies. At sea level, at 59° F, it is 29.92 inches Hg or 760 mmHg. The medical standard is to use mmHg. Atmospheric pressure decreases as you get further away from the surface of the earth and also as temperature increases. The component gases of the atmosphere each exert a consistent partial pressure to the atmospheric pressure. For example:

$$\begin{aligned}\text{Partial pressure } O_2 &= F_i O_2 \times P_b \\ &= 0.209 \times 760 \text{ mmHg}\end{aligned}$$

Table 3-1: Findings in Bronchoalveolar Lavage

Results	Cause
< 1% neutrophils; < 16% lymphocytes; no eosinophils	Normal findings
Increased neutrophils	Idiopathic pulmonary fibrosis (IPF), collagen vascular disease, asbestosis, suppurative infections, granulomatosis with polyangiitis, ARDS
Increased lymphocytes	Hypersensitivity pneumonitis and sarcoidosis
Increased eosinophils	Acute and chronic eosinophilic pneumonia, some ARDS, Churg-Strauss, Löffler syndrome, tropical eosinophilia, parasite infection (esp. ascariasis), TB, collagen vascular disease, malignancy, and drug reactions
Diagnosis of specific types of pneumonias and other infectious diseases	*95% sensitive for PJP in AIDS patients *CMV pneumonia (*inclusion bodies) *Disseminated TB or fungal infection *Diagnosing pneumonia in ARDS patients
Turbid, PAS-positive material	*Alveolar proteinosis
Langerhans cells	*Eosinophilic granulomatosis (histiocytosis x)
Bloody with a large amount of hemosiderin in the alveolar macrophages	*Diffuse alveolar hemorrhage
Hyperplastic and atypical type II pneumocytes	*Cytotoxic lung injury
"Foamy" changes with lamellar inclusions	*Amiodarone-induced disease
* In these, BAL results are sufficient for diagnosis.	

Quick Quiz

- High resolution CT scan is used to diagnose what conditions?
- What are the advantages of helical CT?
- What diseases are associated with a reduced DLCO?

This partial pressure $O_2 = 158.84$ mmHg in the air surrounding us at sea level at 59° F. This pressure is called the P_iO_2 (inspired). This fraction of 20.9% remains constant as atmospheric pressure decreases with increasing altitude.

The following is the **alveolar air equation**. It calculates the partial pressure of O_2 in the alveoli.

$$P_A O_2 = [(P_b - P_{H_2O}) \times F_i O_2] - [P_a CO_2 / 0.8]$$

This equation looks different from the simpler P_iO_2 equation just discussed. The reason is because the partial pressure of inspired gases changes a little when it gets into the damp alveoli, where $O_2 \leftrightarrow CO_2$ exchange occurs. Here, we must account for the additional partial pressure of water vapor P_{H_2O} (= 47 mmHg at sea level) and the shifts in concentrations of O_2 and CO_2 in the alveoli. The respiratory quotient (0.8) is the minute production of CO_2 /minute consumption of O_2 . This quotient allows us to use the measurable $P_a CO_2$ (arterial) in the alveolar air equation instead of the $P_A CO_2$, which we can't readily measure.

So, to get back to the alveolar air equation:

$$P_A O_2 = [(P_b - P_{H_2O}) \times F_i O_2] - [P_a CO_2 / 0.8]$$

We see that the $F_i O_2$ is still multiplied by the P_b but only after its value is decreased to account for the water vapor. The second term will decrease this product by an amount that takes into account the $O_2 \leftrightarrow CO_2$ exchange in the alveoli.

We'll now go over a few other items and then go a little more into this!

Other terms:

$P_a O_2$ = partial pressure of oxygen in the arterial blood. Commonly called the " PO_2 ."

$P_a CO_2$ = partial pressure of carbon dioxide in the arterial blood. Commonly called the " PCO_2 ."

$S_a O_2$ = oxygen saturation of hemoglobin in the arterial blood.

$S_v O_2$ = mixed venous blood oxygen saturation. Mixed venous blood is in the pulmonary artery.

$S_{cv} O_2$ = central venous blood oxygen saturation. This measurement is used in sepsis management.

HYPOXEMIA

Hypoxemia has 6 causes:

- 1) Ventilation/Perfusion (V/Q) mismatch: the main cause of hypoxemia in chronic lung diseases—responds well to 100% O_2 . It may be due to airspace inadequately perfused or perfused areas inadequately ventilated. Examples: asthma, COPD, alveolar disease such as pneumonia, interstitial disease, and pulmonary vascular disease; e.g., pulmonary hypertension or pulmonary embolism. The hypoxemia improves after oxygen administration.
- 2) Right-to-left shunting: seen in ARDS or pneumonia, where hypoxemia is due to perfusion of non-ventilated alveoli. ARDS does **not** respond well to 100% O_2 ; it responds better to positive end-expiratory pressure (PEEP). See Ventilator Support for ARDS on [page 3-66](#). Other causes, besides alveolar collapse: intra-alveolar filling (pneumonia, pulmonary edema), intracardiac shunt, and vascular shunt.
- 3) Decreased alveolar ventilation: seen with decreased tidal volumes or low respiratory rates; e.g., stopping breathing. This **always** has a high $P_a CO_2$ associated with the hypoxemia. The A-a gradient ($D_{A-a} O_2$, discussed next) is normal. Think drug overdose, neuromuscular disease, or CNS disorder.
- 4) Decreased diffusion: actually has **little** causal effect on hypoxemia at rest, but can play a role in exercise-induced desaturations! It takes a **tremendous** amount of thickening of the alveolar-capillary interface to decrease diffusion of O_2 . The carbon monoxide diffusing capacity (**DLCO**) test measures how well inspired CO diffuses from the alveoli to RBC hemoglobin and acts as a surrogate marker for whether diffusion impairment exists for both CO_2 and oxygen. Low DLCO occurs with interstitial lung diseases (**ILDs**) and **emphysema**, in which symptoms improve with supplemental O_2 . Hypoxemia occurs when the DLCO is $\leq 30\%$ of predicted; it may occur at higher DLCO if there is a rapid heart rate. With rapid heart rate, the time for diffusion is limited, so decreased O_2 transfer occurs. **Increased** DLCO is seen with alveolar hemorrhage.
- 5) High altitudes (low $F_i O_2$): results in a reduced $P_A O_2$. $D_{A-a} O_2$ is normal unless lung disease is present.
- 6) Low, mixed venous O_2 ($P_v O_2$): This can decrease the $P_a O_2$ during resting conditions, secondary to the normal shunt that exists ($\sim 5\%$); it will also exaggerate all other causes of low $P_a O_2$.

So, with the above causes of hypoxemia:

- Supplemental O_2 does **not** cause significant increase in $P_a O_2$ with R-to-L shunting or shunt physiology.
- A-a gradient is **normal** with hypoventilation and with high altitudes.

A-a GRADIENT

The alveolar-arterial gradient (A-a gradient), or A-a O_2 ($D_{A-a}O_2$), is the difference between the partial pressure of oxygen in alveoli (A) and that in arterial blood (a):

$$D_{A-a}O_2 = P_{AO_2} - P_aO_2$$

The P_aO_2 is relatively consistent in a group of people in a room. It is the P_aO_2 that varies individually with lung problems. And it is the **difference** between these 2 partial pressures that is the key indicator. And again, $D_{A-a}O_2$ is increased in all causes of hypoxemia **except** hypoventilation and high altitude. In reality, the $D_{A-a}O_2$ is useful only when performed on room air since the gradient will increase as the F_iO_2 increases; it is also hard to know the exact F_iO_2 when a patient breathes with nasal cannula or a poorly fitted face mask.

$D_{A-a}O_2$ is 5–15 in healthy young patients. It increases normally with age and abnormally in lung diseases, causing a V/Q mismatch; i.e., blood flow or diffusion abnormality. Note: A patient with a significant pulmonary embolus invariably has an increased $D_{A-a}O_2$, but, if the patient is hyperventilating (which is common), the ABG may show a normal P_aO_2 !

As mentioned, $D_{A-a}O_2$ increases with age. 2 rules-of-thumb for determining normal $D_{A-a}O_2$ are:

- 1) Normal $D_{A-a}O_2 \leq 0.3 \times \text{Age (years)}$
- 2) Normal $D_{A-a}O_2 \leq (\text{Age}/4) + 4$

To find the $D_{A-a}O_2$, first determine the partial pressure of O_2 in the alveoli (P_{AO_2})—discussed earlier.

$$P_{AO_2} = [(P_b - P_{H_2O}) \times F_iO_2] - [P_aCO_2/0.8]$$

And at standard temperature at sea level:

$$P_{AO_2} = [(760 - 47) \times 0.209] - [P_aCO_2/0.8]$$

$$P_{AO_2} = [149] - [P_aCO_2/0.8]$$

or, to more easily mentally calculate,

$$P_{AO_2} = 149 - 1.25(P_aCO_2)$$

So, getting back to the original formula ...

$$D_{A-a}O_2 = P_{AO_2} - P_aO_2$$

... where the P_aO_2 is obtained from the arterial blood gas. Or, to more easily calculate it mentally, the formula is shifted around to:

$$D_{A-a}O_2 = 149 - [P_aO_2 + (1.25 \times P_aCO_2)]$$

Okay, got this? The P_aCO_2 and the P_aO_2 are read off of the ABG report. If at sea level and inspiring room air, take a **quarter more** than the P_aCO_2 and **add** it to the P_aO_2 , then **subtract** the result from 149.

It is very useful to calculate the gradient for every arterial blood gas you get—and on any blood gas given on the Boards! It helps you quickly identify whether hypoxemia exists because of a problem in the alveolar-capillary unit (e.g., low: pulmonary embolism, pneumonia) or if some other cause is to blame (e.g., normal: decreased alveolar ventilation).

OXYGEN DELIVERY TO TISSUES

What is important to the tissues is how much oxygen they receive. This depends on **both** of the following:

- 1) The amount of oxygen transported to the tissues
- 2) Once this oxygen arrives at the tissues, how much is taken up and subsequently utilized by the mitochondria and/or cells

Oxygen Transport to Tissue

Oxygen **transport** to the tissues = DO_2 . DO_2 = Cardiac output $\times$ Oxygen content of arterial blood (C_aO_2), where

$$C_aO_2 = (1.34 \times \text{Hgb level} \times S_aO_2) + (0.003 \times P_aO_2)$$

(We will ignore the O_2 dissolved in plasma: $0.003 \times P_aO_2$.)

So ...

$$DO_2 = \text{cardiac output} \times (1.34 \times \text{Hgb level} \times S_aO_2)$$

Notice, from this equation, that oxygen transported to the tissues depends on **3** factors:

- 1) Cardiac output.
- 2) Hemoglobin level.
- 3) Hemoglobin saturation (S_aO_2 , **not** P_aO_2 !). This is why the hemoglobin-oxygen (oxyhemoglobin) dissociation curve (and the use of pulse oximetry) is so important.

These are also the 3 factors you look at when a critically ill patient requires better oxygen delivery. In Board questions, you typically are given a critically ill patient with either a low cardiac output or an obvious anemia with an O_2 sat of 90% and P_aO_2 of 60 mmHg. The answer is to address the obviously low Hgb or cardiac output—the P_aO_2 is fine because the S_aO_2 is fine!

Oxyhemoglobin Dissociation Curve

The oxyhemoglobin dissociation curve (or oxygen saturation curve; **Figure 3-1**) typically shows the amount of O_2 saturation of hemoglobin (S_aO_2) for a certain P_aO_2 . It is the amount of O_2 -saturated Hgb that is important. You can see from the graph that, everything else being normal, a P_aO_2 of 60 mmHg results in an S_aO_2 of $> 90\%$.

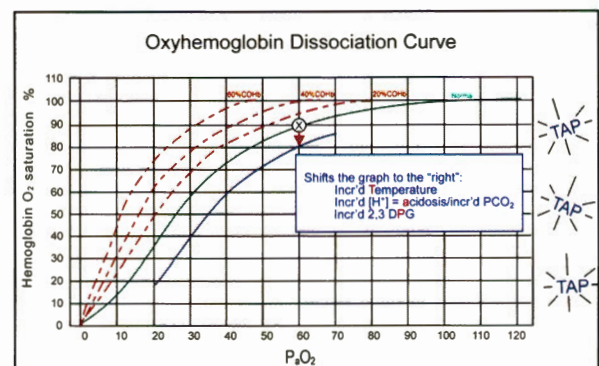


Figure 3-1: Oxyhemoglobin Dissociation Curve

Quick Quiz

- A normal A-a gradient in a hyperventilating patient should make you think of this diagnosis.
- What is a simple formula for calculating the A-a gradient?
- Name 3 factors that, for a specific P_aO_2 , cause a decrease in hemoglobin O_2 saturation.
- What does CO poisoning do to the oxyhemoglobin dissociation curve?
- What are the symptoms that occur at increasing levels of methemoglobinemia? Treatment?

The actual oxygen saturation of a particular hemoglobin molecule at a particular P_aO_2 is dependent on temperature, erythrocyte 2,3-DPG (2,3-diphosphoglycerate) level, and pH status. High or low levels of serum phosphorus cause an increased or decreased 2,3-DPG. The oxyhemoglobin dissociation curve shows the S_aO_2 for a certain P_aO_2 —given variations in these 3 factors (temperature, T; 2,3-DPG [based on phosphorus], P; and pH, A [for acidosis]).

When the graph is shifted to the “right,” it reflects a decrease in Hgb affinity for O_2 (so a decreased O_2 uptake by the Hgb). Decreased affinity promotes off-loading of the O_2 to the tissues.

With a shift to the “left” (with decreased levels of these same factors), it reflects an increased Hgb affinity for O_2 (so an increased S_aO_2 for a particular P_aO_2).

The blue line on the graph indicates what is called a “shift to the right,” but it is more logical to think of it as a “shift down” in which, for a certain P_aO_2 , the S_aO_2 is decreased. On the graph, at a P_aO_2 of 60, the O_2 saturation decreases from 92% to 82% with this right shift.

Note that the TAP, TAP, TAP on the right of the graph is to remind you of the factors that shift the graph to the right—increased Temp, Acidosis, and Phosphorus (rrright, a tap tap ...!).

Carbon monoxide binds tightly to Hgb, preventing O_2 from binding. Additionally, the binding of CO causes the other oxyHgb to bind even more tightly to O_2 —shifting the curve to the left. The typical O_2 saturation tests (e.g., pulse oximeter) do **not** distinguish between oxyHgb and carboxyHgb, so the oxyhemoglobin curve not only shifts to the left but also appears to quickly get 100% saturated. With severe CO poisoning, the majority of Hgb is saturated with CO, leaving little room for O_2 . The **red** tracing shows how the graph would be shifted to the **left** at increasing amounts of COHgb.

Methemoglobin is produced when the iron in the Hgb molecule is oxidized from the ferrous (Fe^{+2}) to the ferric (Fe^{+3}) form, and the resulting methemoglobin molecule cannot hold onto O_2 or CO_2 —with disastrous results to

the tissues. Similar to carboxyhemoglobin, methemoglobin causes regular ferrous Hgb to hold much more tightly to O_2 , thereby shifting the oxyhemoglobin dissociation curve to the **left** (or “up” for a set P_aO_2). Also, like carboxyhemoglobin, typical O_2 saturation tests cannot differentiate oxyhemoglobin from methemoglobin. Net result is a left shift of the oxyhemoglobin saturation curve that climbs to 100% at lower P_aO_2 levels. Again, similar to the COHgb effect but for different reasons.

Methemoglobinemia may be acquired (drugs) or hereditary. Clinical effects of methemoglobinemia:

- > 25% = perioral and peripheral cyanosis
- 35–40% = fatigue and dyspnea begin
- > 60% = coma, death

Treatment for methemoglobinemia is **100% O_2** , remove the cause, and **methylene blue** (which causes rapid reduction of methemoglobin back to hemoglobin). Chronic, hereditary methemoglobinemia is best treated with 1–2 grams daily of ascorbic acid.

Know that the normal oximeter, which measures the absorption of 2 wavelengths of light, is **inaccurate** when there are significant levels of **CO** or **methemoglobin**. You should also know that the oxygen saturation reported on an arterial blood gas analysis is a calculated value, not a measured one. Measuring a true level of the different hemoglobin saturations requires inserting blood into a special CO-oximeter that uses a spectrophotometer to make the measurement of oxygen saturation, methemoglobin, carboxyhemoglobin, and sulfhemoglobin levels. (Lipemic serum results may be inaccurate since the fat potentially interferes with light absorption.)

A newer device, not yet available in most hospitals, measures 8 wavelengths and can identify both methemoglobin and carbon monoxide.

Bottom line: Realize that the standard pulse oximeter, placed at the bedside, is not always helpful in CO poisoning and methemoglobinemia because the value is often normal, and you must order measurement of the various hemoglobins on blood samples.

Oxygen Release to Tissues

Okay, we discussed oxygen transport to the tissues. What about actual oxygen release to the tissues? Here again, we look at the oxyhemoglobin dissociation curve as it applies to oxygenated blood in the tissues. Any factor that shifts the graph to the right/down reflects a decreased affinity between oxygen and hemoglobin and, in the local tissue environment, causes a release of oxygen to the tissues.

E.g., working muscles: In the area of the capillaries of working muscles, there is an increase of pCO_2 due to normal metabolism → **local acidosis** → decreased affinity of Hgb for O_2 → release of O_2 to the tissues (Bohr effect).

E.g., RBCs: RBCs produce **2,3-DPG** as a byproduct of anaerobic metabolism. (All RBC metabolism is

anaerobic.) The more 2,3-DPG there is, the more O_2 is released from the Hgb for use by the RBCs. Similarly, patients with chronic anemia have increased 2,3-DPG.

Blood stored > 1 week has a decreased level of 2,3-DPG, and large transfusions of this blood result in a “shift to the left.”

When there is **systemic acidosis** (or high temp or high 2,3-DPG), the decrease in affinity for O_2 by Hgb results in less O_2 picked up by the Hgb in the lung, as well as more O_2 released in the tissues. So, although the Hgb O_2 saturation (S_aO_2) is lower for a certain P_aO_2 , more of the oxygen carried by the hemoglobin is released to the tissue. The net result is to dampen the effect of low S_aO_2 caused by acidosis, high temp, and high 2,3-DPG. It dampens but does not negate or reverse the effect.

Conditions that shift the graph to the left (alkalosis, low temp, low 2,3-DPG) work similarly, although more O_2 is bound by the Hgb, and less is released to the tissues. Again, it dampens but does not negate the effect.

DLCO

Carbon monoxide diffusing capacity (DLCO) is **decreased** by anything that interrupts gas-blood O_2 exchange.

Decrease in DLCO implies a loss of effective, capillary-alveolus interface. It is usually due to loss of alveolar-capillary units, as seen in **emphysema**, **interstitial lung disease**, and **pulmonary vascular** diseases. **Anemia** also causes a decrease in DLCO.

Know that the DLCO is the 1st parameter to decrease in interstitial lung disease; thus, it should be followed when prescribing potentially dangerous medications such as amiodarone or lung-toxic chemotherapy. Also, DLCO may be the only abnormal pulmonary function parameter in pulmonary vascular disease.

Normal DLCO is usually seen in asthma and chronic bronchitis because, although there is bronchoconstriction, there is **no** alveolar disease. Therefore, recognize that the DLCO is the major pulmonary function parameter that helps you to distinguish **emphysematous** COPD (**low** DLCO) from chronic bronchitis and asthma (normal DLCO).

Increased DLCO is seen in problems that increase effective blood flow to the functional lung, such as heart failure, diffuse alveolar hemorrhage, pulmonary infarction, and idiopathic pulmonary hemosiderosis (IPH).

LUNG VOLUMES AND PULMONARY FUNCTION TESTS

Overview

In your office, with spirometry, you can determine most of the lung volumes and capacities, expiratory flows, and flow-volume loops and also assess bronchodilator response.

A pulmonary function lab is needed for:

- Total lung capacity determination
- DLCO determination
- Methacholine or other challenge tests

For the lung volumes discussed below, generally **< 80%** is abnormal, and **> 120%** may also be significant.

When reviewing PFTs, keep in mind the following:

- Total lung capacity (**TLC**) is used to assess **interstitial** lung disease (i.e., TLC is decreased in intrathoracic restrictive lung disease).
- Expiratory flow rate (**FEV₁/FVC**) is used to assess **obstructive** lung disease. Airway obstruction is diagnosed when the FEV₁/FVC is **< 0.7 (70%)**. To be very specific and avoid over-diagnosis of obstructive lung disease, many pulmonologists in practice are now using the predicted 95% confidence interval to diagnose a reduction in the FEV₁/FVC ratio. General internists just need to know the 70%.

Lung Volumes

Review the Lung Volumes diagram (Figure 3-2). There are 4 basic functional volumes of which the lung is made:

- 1) Residual volume (**RV**) = unused space
- 2) Expiratory reserve volume (**ERV**) = from full non-forced end-expiration to full forced end-expiration
- 3) Tidal volume (**V_T**) = used in normal unforced ventilation
- 4) Inspiratory reserve volume (**IRV**) = from normal unforced end-inspiration to full forced end-inspiration

A “capacity” is 2 or more of these basic volumes and gives even more functional significance to them. E.g., vital capacity (VC) is the volume you have available for breathing (makes sense) and is composed of the IRV + V_T + ERV. The total lung capacity (TLC) is composed of the VC + RV.

In severe COPD, TLC is normal or increased (even though vital capacity is decreased) due to a greatly increased RV—seen as barrel chest.

In restrictive disease, the TLC is decreased due to both a decreased VC and RV.

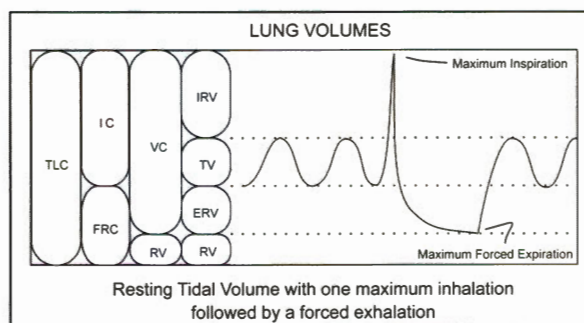


Figure 3-2: Lung Volumes

Quick Quiz

- What is vital capacity (VC), and what smaller lung volumes make up VC?
- Characterize the differences in the flow-volume loops for restrictive and obstructive (dynamic and static) airway diseases. (See Figure 3-5.)

TLC is determined in the lab by helium dilution, nitrogen wash-out, or plethysmography. Use plethysmography for patients with airflow obstruction.

The tracing in the Lung Volumes diagram shows a forced expiration from maximum inspiration. The next diagram (Figure 3-3) shows a comparison of similar expirations for patients with normal, obstructive, and restrictive airways. This is an easy and important test, but usually you will not see it diagrammed this way.

Although the TLC cannot be determined from spirometry (must know the RV), you can determine the degree of **obstruction** by comparing the forced expiratory volume at 1 second (FEV_1) to the forced vital capacity in the ratio FEV_1/FVC ($FVC = VC$ during a forced expiration).

In a patient with a normal lung, the ratio is about 0.8. It is always less in a COPD patient or an asthma patient having an acute attack, but it may be normal or increased in a patient with restrictive disease—even though the VC is small—because this patient has no trouble getting air out.

A patient with asthma has reversible disease and, if not having an acute attack, may have a normal FEV_1/FVC .

Flow-Volume Loops

The diagrams of flow-volume loops shown are a more common way of expressing airflow in the different lung diseases—again, these are derived from the spirometry data and are calculated and plotted by an attached computer, where the FEV_1/FVC is automatically determined. Note that the y-axis is flow rate.

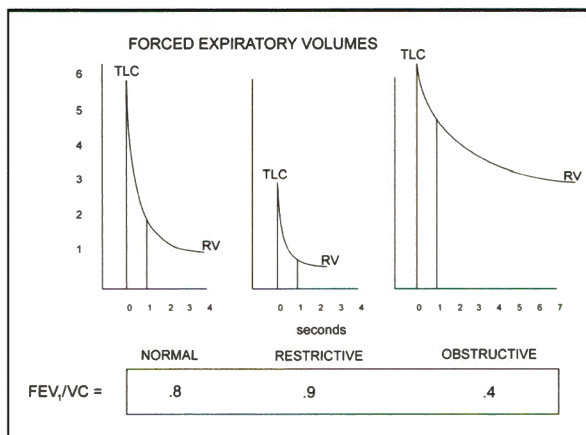


Figure 3-3: Forced Expiratory Volumes and FEV_1/FVC

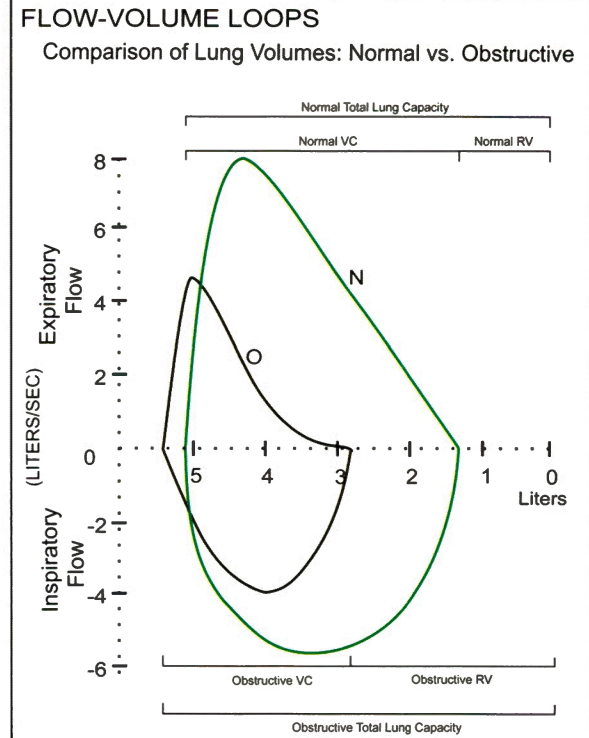


Figure 3-4: Flow-Volume Loops — Obstruction

Because we cannot determine residual volume (RV) from spirometry, we get most of our information by the **shape** of the loop. The exception is in restrictive disease; the shape is similar to normal, but the vital capacity ($= TLC - RV$; width) is much smaller than normal.

Figure 3-4 compares obstructive vs. normal lung flow loops. Figure 3-5 includes restrictive diseases. Know the shapes and sizes of these loops!

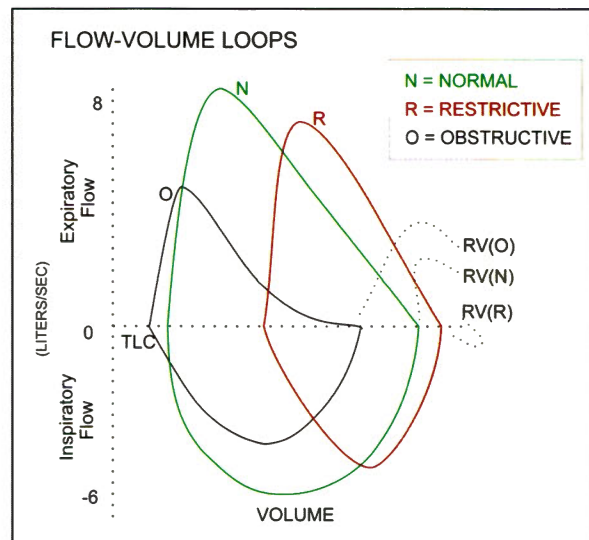


Figure 3-5: Flow-Volume Loops — All

In obstructive disease, **Figure 3-4**, increased expiratory airway resistance causes decreased expiratory flow rate. Again, while normal $FEV_1/FVC = 80\%$, obstruction is defined as **< 70%**. (In severe obstruction, it may be only 40%!) Additionally, there is a scooping of the tracing in the latter half of expiration. Causes of lower airway obstruction include asthma, COPD, bronchiectasis, and cystic fibrosis.

Restrictive disease. Notice that **Figure 3-5** shows intrathoracic (parenchymal; ILD) restrictive disease in which residual volume (RV) is always decreased. Extrathoracic restrictive disease states (e.g., obesity, kyphosis) may have a normal RV, but shape and size are similar.

Bronchodilator response during pulmonary function testing is done for 2 reasons:

- 1) To determine if the obstruction is responsive to beta-agonists. Before testing, withhold beta2-agonists for 8 hours and theophylline 12–24 hours.
- 2) To test for efficacy of current regimen. In this case, medications are not withheld. If treated patients have a response to beta2-agonists, it suggests they are not on an optimum regimen.

Methacholine or other bronchoprovocation-challenge testing is done in people with normal spirometry and intermittent asthma-like symptoms, or other symptoms suggestive of airflow obstruction, to determine if they have **bronchial hyperreactivity**. This test is often done in the workup of **chronic cough** (see Asthma on [page 3-10](#)) and occasionally in patients with cold air-induced exercise-related bronchospasm.

Inhaled methacholine (or histamine or cold air) is given to the patient while monitoring for a drop in FEV_1 . Know that asthmatics will bronchoconstrict at a **very low dose** of the irritant, whereas non-asthmatics will not.

Also know that PFTs are always the first test in the evaluation of a possible asthmatic, and bronchoprovocation is done **only** when initial **PFTs are normal**.

Pre-Op

PFTs are **not** indicated in the routine pre-op exam.

PFTs + ABGs **are** indicated in the following circumstances:

- If the surgical procedure is close to the diaphragm (gallbladder, etc.).
- If the patient has moderate or worse lung disease. In these cases, an $FEV_1 < 1\text{ L}$ or an **elevated pCO_2** indicates that the patient is at risk for post-op pulmonary complications.
- For lung **cancer** or lung **resection** pre-surgical evaluation. Assuming a worst-case scenario (pneumectomy), the patient must still have adequate lung function post-op. High risk of post-op morbidity is indicated by a predicted $FEV_1 \leq 0.8\text{ L}$ after surgery. In a patient with a pre-op $FEV_1 \leq 1.6\text{ L}$, you can

estimate the post-op FEV_1 by doing split-lung PFTs (hard to do), obtaining a quantitative ventilation, or by quantitative perfusion lung scan. Then multiply the % perfusion (or ventilation) of what will be left after surgery by the FEV_1 to obtain the estimated post-op FEV_1 .

Now, let's first look at what PFTs show in the major lung diseases. In subsequent discussions, we focus on the clinical aspects of the major lung diseases.

PFTs for Specific Lung Diseases

1) Emphysema:

- Decreased expiratory flow volume (shortened height of top portion of the flow-volume loop).
- Concave expiratory flow-volume loop tracing.
- Minimal response to beta2-agonist: **< 12%** improvement or **< 200 mL** improvement in FEV_1 or FVC.
- Increased TLC, reduced VC = hyperinflation with trapped air.
- DLCO is **decreased** (the destruction of alveolar-capillary interface—suggests emphysema).

2) Chronic bronchitis:

- Decreased expiratory flow volume (shortened height of top portion of the flow-volume loop).
- Concave expiratory flow-volume loop tracing.
- Minimal response to beta2-agonist: **< 12%** improvement or **< 200 mL** improvement in FEV_1 or FVC.
- Normal or only slight increase in TLC = normal or slightly reduced VC.
- DLCO is **normal** to slightly decreased, but it is much lower in emphysema. Remember DLCO is the test that allows you to differentiate emphysema from chronic bronchitis and asthma. Understand that most cases of COPD have mixed physiology with components of both chronic bronchitis and emphysema.

3) Asthma:

- PFTs may be normal if no active disease.
- Decreased expiratory flow (shortened height of top portion of the flow-volume loop).
- Concave expiratory flow-volume loop tracing.
- Significant response to beta2-agonist.
- Normal or increased TLC (due to hyperinflation) and normal or reduced VC.
- DLCO is **normal**.

4) Interstitial lung disease:

- Normal to increased FEV_1/FVC .
- Straight or slightly convex expiratory flow-volume loop tracing.
- Proportional decrease in all lung volumes.
- DLCO is **reduced** (due to thickening of the alveolar-capillary interface) and is the first pulmonary parameter to change with disease progression.

Quick Quiz

- When is methacholine bronchoprovocation testing performed?
- What are the results of these lung tests in patients with obstruction: VC, TLC, FEV₁, FEV₁/FVC, RV?
- What are the results of these lung tests in patients with restriction: VC, TLC, FEV₁, FEV₁/FVC, RV?
- What is the DLCO in asthma? In emphysema? In interstitial lung diseases?

Now some examples. When evaluating a PFT scenario, think in terms of:

- Expiratory flow
- Lung volumes
- Diffusion capacity
- Response to bronchodilators

Also consider that anything < 80% of normal is an abnormal finding. (FEV₁/FVC is already age-adjusted, and % predicted is sex, age, and height adjusted.)

Approach to PFT results analysis. We will be using Table 3-2 during this discussion. Remember, we are basically looking for normal, restrictive, or obstructive disease. Each time you figure out a line, label it.

1) Look for all normals:

Circle everything $\geq 80\%$ —these values are “normal.” If all values are $\geq 80\%$, the results are normal. Label it “normal.” Remember that most smokers have **normal** values.

2) Look for restrictive disease:

Any TLC < 80% is, by definition, restrictive. Label these results as “restrictive.” If TLC is not known, restrictive disease is reflected in a proportional decrease in FEV₁ and FVC (i.e., FEV₁/FVC = 80% but FVC is < 80%).

If restrictive, check the DLCO. This will determine if it is extrathoracic or intrathoracic:

- If the decrease in DLCO is **proportional** to the decrease in TLC, it means that the restriction is not due to parenchymal disease—rather, it is of extrathoracic origin. Label it “**extrathoracic**” and think of obesity and kyphosis.
- If the decrease in DLCO is **disproportionately low** compared to the decrease in TLC, label it “**intra-thoracic**” and think of interstitial lung disease.

3) Look for obstructive disease:

Obstruction is defined by a disproportionately low FEV₁. So both FEV₁ and FEV₁/FVC are low. Label these lines “obstructive.”

If obstructive, check the TLC, DLCO, and reaction to beta2-agonists:

- “Emphysema” if the TLC is high but the DLCO is low. Minimal-to-no response to beta2-agonist.
 - “Asthma” if the DLCO is normal, or there typically is a reaction to beta2-agonist.
- 4) Others are combinations of obstructive and restrictive diseases. Especially seen in patients with combined problems (asthma + obesity) or with certain lung diseases, especially sarcoidosis, eosinophilic granuloma (histiocytosis X), and lymphangioleiomyomatosis.

Okay, let's apply this to a table of PFT results [**Know!**]. In your practice (or on your Boards), you may or may not have these same test results. Table 3-2 reviews some PFT results as a percentage of predicted. Remember that, in general and especially for the Boards, < 80% of predicted is abnormal.

#1 You should have all these values circled. These are, of course, normal. Remember that normal results are seen in most smokers!

#2 Extrathoracic restrictive mechanics (i.e., non-parenchymal). All restrictions, intra- and extrathoracic, are defined by a decrease in TLC. That there is no obstructive mechanism involved is shown by the maintenance of the FEV₁/FVC ratio: The FEV₁ is decreased in proportion to the decrease in FVC, so the FEV₁/FVC is $\geq 80\%$. The **extrathoracic** involvement is indicated by the proportional decrease in TLC and DLCO—that is, the decrease in DLCO is due to the decrease in TLC. Pure extrathoracic restriction is seen with **kyphosis** and **obesity**. Although kyphoscoliosis occurs in a small percentage of neurofibromatosis patients (von Recklinghausen disease) and may be due to tuberculosis involving the thoracic vertebrae, it is usually a result of compression fractures of the thoracic vertebral bodies, secondary to long-standing osteoporosis.

If a patient is 1–3 days post-CABG and suffering from orthopnea, check the PFTs, but also check FVC both standing and lying down. If the patient has extrathoracic restrictive mechanics and the difference in FVC is > 20% (decreases

Table 3-2: PFT Analysis Table

	% FEV ₁	% FVC	% TLC	% DLCO
1	83	89	92	85
2	58	62	68	64
3	52	80	110	65
4	55	87	100	88
5	57	82	70	68
6	66	72	75	66

with lying down), consider bilateral diaphragmatic paralysis from the cold cardioplegia. (This is for Board questions—a chest x-ray could have told you this!)

Unilateral phrenic nerve problems can be diagnosed by a “sniff test” with fluoroscopy. Also note that a decrease in FVC (from standing to lying) in the high-normal range (15–20%) is commonly seen with obesity. The DLCO could be disproportionately low (say, 54%) if this post-CABG patient also had some post-op atelectasis.

Question: Besides cold cardioplegia, what are other possible causes of bilateral elevated hemidiaphragm? Answer: poor inspiration, SLE, bilateral phrenic nerve paralysis (spine injury, tumor, neurological disorder), diaphragmatic weakness from ALS, large-volume ascites, and bilateral subpulmonic effusions. These all make sense, so just think about them, but don’t memorize them!

#3 Pure obstruction with low DLCO and a high TLC. The FEV_1/FVC is $< 80\%$. The TLC is high and the DLCO is disproportionately low, indicating a loss of alveolar-capillary units. Most probable etiology is emphysema—from either smoking or α_1 -antitrypsin deficiency.

#4 Pure obstruction with normal DLCO. Same as #3, except the DLCO is normal, indicating asthma. In both #3 and #4, you may find a low FVC if the obstruction is so severe the patient does not have enough time to fully expire before getting short of breath, but the FEV_1/FVC remains $< 70\%$.

#5 Combined obstruction and extrathoracic restriction. The low FEV_1/FVC indicates obstruction. The low TLC indicates restriction, while the proportionate decrease in DLCO narrows it to an extrathoracic etiology. Possible etiologies: an obese patient with asthma or an osteoporotic kyphotic patient with asthma.

#6 Intrathoracic restriction. As in extrathoracic restriction, the FEV_1 and FVC are **proportionately low** (so $FEV_1/FVC > 80\%$). Contrary to extrathoracic restriction, in intrathoracic restriction the DLCO is disproportionately lower than the decrease in TLC. Intrathoracic restriction is seen with many interstitial lung diseases.

OBSTRUCTIVE LUNG DISEASES

ASTHMA

Overview

Asthma is an **inflammatory** condition of the airways with a multifactorial etiology and varying presentation. Patients can have intermittent or persistent and acute or chronic manifestations. The primary manifestation is recurrent episodes of wheezing due to bronchoconstriction—usually reversible either spontaneously or with treatment.

Causes of Asthma

Asthma typically develops early in life. Development of asthma appears to be a complex interaction of mainly 2 factors:

- 1) Host factors (especially **genetic** susceptibility). The role of genes is complex and not well defined at this point. Some asthma is IgE-mediated. **Atopy** is the strongest identifiable predisposing factor for developing IgE-mediated asthma.
- 2) Exposure to certain **environmental agents** at critical points in immune development. **Triggers** are environmental factors that may be the cause of asthma or that induce worsening symptoms when the airways are hypersensitive. Triggers can be broadly categorized into 6 areas: allergens, irritants, chemicals, respiratory infections, physical stress, and emotional stress. Both airborne **allergens** and viral respiratory **infections** play important roles in the **development** of asthma in susceptible people. Other environmental agents associated with the development of asthma are pollution, tobacco smoke, and airborne agents prevalent in certain occupations. These have not been studied as much as allergens and viral infections.

The cause of asthma is often not discovered, especially in adult-onset asthma.

Some specifics: occupational causes (isocyanates are most common!), cotton dust (byssinosis), formaldehyde, volatile organic compounds, toluene diisocyanate, fluorocarbons, grain dust, and wood dust (especially western cedar). But **not** silica! Unvented gas stoves release NO_2 —which worsens asthma.

Occupational asthma may be IgE-dependent, which causes an early or biphasic reaction, or IgE-independent (late reaction). Both smoking and a history of atopy are important sensitizing factors for occupational asthma.

Patients with ASA-sensitive asthma often have the **asthma triad (Samter’s triad)**: ASA-sensitivity + asthma + nasal polyposis. Patients are young to middle-age adults. Symptoms start with rhinitis or congestion and progress to asthma. Then polyposis. Then ASA sensitivity. ASA sensitivity can be extreme (anaphylaxis). ASA-sensitive asthmatics may also be sensitive to other NSAIDs and tartrazine dyes but **not** to **sodium** or **choline** salicylates.

Allergic rhinitis and asthma are both systemic inflammatory conditions that affect upper and lower airways and may reflect a spectrum of the same disease. Up to 80% of people with asthma have rhinitis. Treatment of allergic rhinitis with intranasal glucocorticoids improves asthma symptoms and decreases emergency department visits and hospitalizations.

A very interesting aspect of asthma is its relationship to GE reflux, although it is incompletely understood. A lot of asthmatics have GERD, and past data have supported

Quick Quiz

- What is the difference in the DLCO in intrathoracic restriction versus extrathoracic?
- What skin finding is a predisposing factor for IgE-mediated asthma?
- What is the “asthma triad”?
- What are the comorbidities that may exacerbate asthma?
- In the management of asthma, initial treatment is based on _____. After therapy is started, focus is on _____.
- What spirometry findings are required to diagnose asthma?
- How can you diagnose exercise-induced bronchospasm?

the idea that uncontrolled asthma can result when reflux is untreated. In fact, pH probe studies show that many asthmatics have esophageal reflux without having reflux-type symptoms. Smaller studies have driven the conclusion that uncontrolled asthmatics should be treated for possible asymptomatic GERD. Even the recent 2007 asthma guidelines recommend empiric treatment for GERD in patients with uncontrolled asthma, whether or not they are symptomatic.

Later data, however, showed that empiric treatment of **asymptomatic** GERD with a proton pump inhibitor did **not** affect **asthma** outcomes in patients with inadequately controlled asthma.

So, while there is an association between GERD and asthma, the relationship has controversial elements.

Asthma is exacerbated by comorbid conditions:

- Allergic bronchopulmonary aspergillosis (ABPA)
- Obstructive sleep apnea-hypopnea (OSA)
- Stress

Changes in the Lung with Asthma

This airway inflammation, whatever the etiology, causes a nonspecific airway **hyperresponsiveness** → airway **edema** and **bronchoconstriction**. Persistent airway inflammation leads to **remodeling** of the airways with fibrosis and muscular hypertrophy, resulting in a continuous nonresponsive airflow obstruction as a component of the clinical picture.

Acute Exacerbation of Asthma

Early in an asthmatic attack, bronchospasm is the major factor; but later on, increased airway inflammation, airway edema, and airway secretions with possible

mucous plugging may dominate—especially suspect this in status asthmaticus.

Asthmatics usually have episodes of some combination of dyspnea, cough, and wheezing; but, on the initial presentation, the patient may have complaints only of a **chronic cough**. (Remember: Patients with GERD may also present with cough, but a nonasthmatic cough due to GE reflux disease occurs typically when supine.)

Regarding patients with a fatal asthma attack, the main factor in mortality is the amount of auto-PEEP they experience (discussed under Intubation on [page 3-16](#)).

Diagnosis of Asthma

Severity of asthma is the basis for treatment at an untreated patient's initial evaluation.

After initial therapy is started, focus on **control** and response to treatment, rather than severity.

Severity of airflow obstruction is categorized as intermittent, mild persistent, moderate persistent, and severe persistent. Any severity level can have exacerbations—which in turn may be mild, moderate, or severe. See Initial Severity column of [Table 3-3 on page 3-14](#).

For diagnosis, the patient must demonstrate at least partially **reversible bronchospasm** and a **history** compatible with asthma. Only if these are not demonstrated do you do a challenge test to induce bronchospasm.

FEV in 6 seconds (FEV₆), FVC, and FEV₁/FVC, before and after use of a bronchodilator, are in the workup of all patients > 5 years old. Response to a short-acting bronchodilator is defined as an increase in the FEV₁ of ≥ 12% and an increase of at least 200 mL.

Bronchoprovocation tests are done in a patient who has **normal** spirometry and 1 or more of the following:

- **Chronic cough**
- Intermittent symptoms of cough/wheeze
- Exertional dyspnea of unknown cause

Methacholine challenge, **histamine** challenge, and **thermal** (cold air) challenge can be used to confirm the diagnosis of asthma. These work on the principle of nonspecific hyperirritability. For the diagnosis of asthma (requires “reversible bronchoconstriction”), the patient must both tighten up with the challenge and loosen up with subsequent bronchodilators. Tests may be coupled (2 or 3 tests at once) with a high index of clinical suspicion for asthma.

Exercise-induced bronchospasm (**EIB**) is diagnosed by a decrease in FEV₁ of ≥ 10% after graded exercise on a treadmill or a stationary bicycle. Patients who have exercise-induced bronchospasm that is exclusively elicited by cold air can have false-negative exercise tests. Bronchoprovocation using methacholine, cold air, or eucapnic voluntary hyperventilation is useful to diagnose this cold air-induced EIB and for patients who might otherwise have a false-negative exercise test.

Treatment of Asthma

Overview

Patients with persistent asthma should have their environment assessed for untreated irritants and allergens. This includes looking for seasonal variation of symptoms, home and workplace evaluation, and skin testing.

The most effective treatment for most asthma is stopping exposure to any **environmental agents** that act as triggers. The goal should be to remove the trigger entirely, but when unable, the patient should minimize contact. Alternatively, the patient can take extra bronchodilator inhalations before exposure—a common way to handle unavoidable triggers such as visiting a house with a pet.

Because of the association of GERD and allergic rhinitis with asthma, the 2007 guidelines recommend empiric medical management for these conditions when patients have difficult-to-control asthma.

For GERD:

- Avoid intake of foods that lessen lower esophageal sphincter tone; e.g., alcohol, caffeine, nicotine, and peppermint
- No eating within 3 hours before bed
- Elevate the head of the bed
- Treat with proton pump inhibitors (PPIs)

Treat rhinitis with intranasal steroids.

Comorbid ABPA, OSA, and stress should be addressed.

Monitor peak expiratory flow (PEF; or peak expiratory flow rate [PEFR]) in those with **moderate-to-severe** asthma and/or in patients who cannot reliably describe symptoms of an exacerbation.

Note that **symptom-based** monitoring is as effective as PEF in **all other** groups.

Prescribe pharmacologic treatment when needed. We will categorize these medications into “quick relief” and “long-term control” categories.

Quick relief (for acute exacerbations and mild, intermittent disease):

- Short-acting beta2-agonists (SABAs)
- Systemic corticosteroids
- Anticholinergics

Long-term control:

- Inhaled corticosteroids (ICS; most potent and most effective)
- Long-acting beta2-agonists (LABAs)
- Mast-cell stabilizers (cromolyn sodium and nedocromil)
- Leukotriene modifiers
- Methylxanthines (theophylline)
- Immunomodulators (omalizumab = anti-IgE)

The following text is a review of these drugs followed by the recommended treatment regimens (Table 3-3 through Table 3-5).

SABAs

The inhaled, short-acting beta2-agonist, albuterol, is the first choice for “rescue” treatment of an acute exacerbation, even if the patient routinely uses them at home.

For chronic asthma treatment, albuterol is indicated for patients who have intermittent symptoms. Know that SABA use of > 2 days/week indicates “poor control” of symptoms, and treatment should be intensified.

Systemic Corticosteroids

Oral corticosteroids (OCS) are an effective, **short-term** treatment for acute asthma. They potentiate the effect of beta2-agonists and have an antiinflammatory effect that has been shown to decrease the frequency of return visits to the emergency department (ED).

OCS are indicated in the acute treatment of asthma when peak flow is < 80% after 3 treatments of rescue SABAs.

Oral steroids have near complete bioavailability and onset of action within 1 hour, so they can be used instead of IV, if the patient is not vomiting. Current preparations taste awful (liquid is so bad that it sometimes causes vomiting), so know that IM injections are equivalent to an oral dose.

IV steroids should be used in respiratory failure.

Chronic administration of OCS for asthma should be prescribed by fellowship-trained asthma specialists and only under strict circumstances because of side effects. The asthma algorithm does not include chronic oral steroids until Step 6 after institution of all other therapeutic options.

Anticholinergics

Ipratropium bromide is the short-acting drug, and tiotropium is the long-acting drug. Only ipratropium is used in asthma treatment. Long-acting anticholinergics are used in COPD.

Anticholinergics cause a decrease in cGMP that relaxes contractions of bronchial smooth muscle. They are usually given along with beta2-agonists for acute exacerbations of asthma/COPD.

For acute asthma, the 2007 guidelines limit the use of ipratropium to ED management of **moderate-to-severe** exacerbations, in combination with **SABAs**. Ipratropium is **not** recommended for use in managing hospitalized asthma exacerbations.

Anticholinergics are **not** used in the **chronic** treatment of asthma.

Oxygen

Oxygen is given during an exacerbation of asthma with a goal of keeping the P_aO_2 of at least 60 mmHg or O_2 sat $\geq 90\%$.

Quick Quiz

- Describe the relationship between symptom-based monitoring and peak expiratory flow rate.
- What is the short-acting drug of choice for asthma exacerbations?
- OCSs are recommended if peak flow is < ___% after ___ treatments with rescue SABAs.
- According to the expert panel guidelines, when is ipratropium used during a hospital stay to treat an asthma exacerbation?
- What is the preferred drug for chronic treatment of persistent asthma?

Inhaled Corticosteroids (ICS)

An **ICS** is the **preferred drug for chronic treatment** of persistent asthma when symptoms are not controlled with SABAs. Why is this? Asthma is an inflammatory process, and inhaled corticosteroids subdue the inflammation where it occurs—with minimal side effects. Beta2-agonists are merely bronchodilators and provide only symptomatic treatment.

Twice-per-day inhalations of corticosteroids are as effective as qid. Know that the dose-response curve for inhaled steroids is flattened in patients with mild persistent asthma (more is not better), so low doses are most effective in this group. But, in “severe persistent” asthmatics, the dose-response curve is not flattened, and this group may benefit from increasing the steroid dose early in treatment.

A spacer greatly reduces the amount of drug deposited in the oropharynx (large particles are trapped in the spacer), thereby decreasing systemic effects from swallowed drug. A spacer also increases the amount of drug reaching the lungs.

ICS and safety:

- There is little, if any, effect on the pituitary-adrenal axis.
- No increase in fractures.
- Cataracts and glaucoma are much less of a problem with ICS than OCS.
- Budesonide is the preferred inhaled steroid in pregnancy. (All other steroids are category C; it is recommended to continue these agents if patients are well controlled with them prior to pregnancy.)
- May cause easy bruising in elderly patients.
- May cause slowing of growth in children, but there is a catch-up period resulting in normal height.
- Higher doses cause oral thrush and dysphonia and have been implicated in recurrent pulmonary infections.

LABAs

Like SABAs, LABAs (salmeterol, formoterol) induce an increase in cAMP, which results in relaxation of the bronchial smooth muscles. Unlike SABAs, however, LABAs cause a sustained effect. Still, LABAs do not address the inflammatory component of asthma, and as such, they are recommended only **after** ICS in the treatment guidelines.

LABAs are indicated for treatment of moderate-to-severe persistent asthma after initial therapy with SABA + ICS. LABAs are not recommended for mild asthma or acute treatment.

LABAs should **never** be used as monotherapy. They should always be added to inhaled corticosteroids! LABA monotherapy increases exacerbations and mortality. The data is so concerning that many pharmaceutical companies have combined LABA with ICS in a single inhaler, so patients cannot inadvertently increase their use of LABA. This issue of how LABAs affect mortality and exacerbations is not settled.

Know that you should never use LABAs as the sole drug for chronic asthma management, and that LABAs are recommended as an add-on drug in an asthma regimen for patients who are uncontrolled on a SABA + an ICS.

LABAs can be used to treat exercise-induced bronchospasm (EIB), but only if the patient does not require daily treatment. If medication is needed daily, the preferred drugs are inhaled albuterol or cromolyn ~ 15 minutes prior to exercise.

Mast Cell Stabilizers

Cromolyn sodium and nedocromil (Tilade®) are **mast cell stabilizers** and act by inhibiting degranulation of mast cells. They have **mild antiinflammatory** effect from decreasing the release of inflammatory mediators.

These drugs are considered 2nd line for use after prescription of the preferred drugs (SABAs, ICS, and LABAs). No toxicity.

Inhaled cromolyn is an alternative to inhaled albuterol for daily control of exercise-induced bronchoconstriction.

Leukotriene Modifiers

Leukotrienes are potent chemical mediators released from mast cells, basophils, and eosinophils. They are potent:

- Smooth muscle contractors
- Promoters of mucus production
- Causes of airway edema
- Vasoconstrictors
- Stimulators of more arachidonic acid release

Montelukast (Singulair®) and **zafirlukast** (Accolate®) are leukotriene-receptor antagonists and **zileuton** (Zyflo®) is a 5-lipoxygenase pathway inhibitor.

Leukotriene modifiers are less potent than ICS and are not as effective as LABAs. They are more often used in children and are **never** the preferred treatment in adults.

Leukotriene modifiers also have some utility in treating patients with EIB, but they are effective in only ~ 50% of patients. Patients with aspirin allergy are more likely to benefit.

Rarely, a patient treated with a leukotriene modifier may develop an eosinophilic vasculitis, termed Churg-Strauss, during a period of corticosteroid withdrawal. This vasculitis is discussed more on [page 3-31](#).

Methylxanthines

Theophylline, a methylxanthine, is less effective than beta₂-agonists. Mechanism of action is bronchodilation and mild antiinflammatory activity brought about through inhibition of phosphodiesterase. Unfortunately, the dose-response curve for theophylline is log-linear; therefore, the drug has a narrow therapeutic index and increased risk for toxicity.

Theophylline is **not** recommended for **acute** treatment of any asthma exacerbation (including in-hospital management) because the benefit does not exceed the risks of toxicity and drug interactions.

For chronic treatment, theophylline is indicated as an adjunct to ICS for difficult-to-control asthmatics, but know that theophylline + ICS is inferior in efficacy to the

combination of a LABA + an ICS. Theophylline is also an alternative to ICS (but is not as effective) for patients who simply cannot use inhalers or have a serious aversion to them.

Definitely know the theophylline toxicity and drug interactions. Ideally, theophylline should be given as a sustained-release preparation, and the serum concentration should be maintained in the therapeutic range of 5–15 mcg/mL. Toxicity symptoms include nausea and vomiting (first symptoms), headache, tremulousness, and palpitations. Toxic patients die or suffer morbidity from seizures, hypotension, and cardiac arrhythmias.

The list of drug interactions with theophylline is long but important. Board-relevant interactions to remember include:

- Increases theophylline levels (causing toxicity): ciprofloxacin, clarithromycin, zileuton, allopurinol, methotrexate, estrogens, propranolol, and verapamil
- Decreases theophylline levels (possibly exacerbating asthma): various antiepileptic drugs, rifampin, St. John's Wort, smoking (more of an issue when patients stop smoking and theophylline levels subsequently increase on the same dose)
- Decreases level of coadministered drug: phenytoin and lithium

See the General Internal Medicine section, Book 5, for an in-depth discussion on theophylline toxicity, including treatment.

Table 3-3: Initial Tx and Maintenance Tx for Patients ≥ 12 years of age

Factors used in the determination of both SEVERITY (with initial eval) and CONTROL level (when on continuing treatment)					Initial evaluation: Treatment is based on SEVERITY		Continuing therapy: Treatment is based on CONTROL	
Days with Sx	SABA use (control only)	Nighttime awakenings	FEV ₁ or PEF ***	Impairment of activity	SEVERITY	Treat per Step level:	CONTROL level	Changing Tx based on CONTROL level
≤ 2 days/week	≤ 2 days/week	< 2/month	≥ 80%	None	Intermittent	Step 1	Well controlled	Maintain current Step
> 2 days/week but not daily	> 2 days/week but not daily and not more than 1x on any given day	3–4/month	≥ 80%	Minor limitation	Mild Persistent	Step 2	Well controlled	Maintain current Step
Daily	Daily	> 1/week but not nightly	> 60%, < 80%	Some limitation	Moderate Persistent	Step 3	Not well controlled	Step up 1 Step Reevaluate in 2–6 wks
Throughout the day	Several times per day	Often 7/week	≤ 60%	Extremely limited	Severe Persistent	Step 4–5	Very poorly controlled	Consider short course of oral corticosteroids Step up 1–2 Steps Reevaluate in 2 weeks

***Use **only** FEV₁ for **initial** evaluation. Use either FEV₁ or PEF for determining control and continuing therapy.

Quick Quiz

- What are signs and symptoms of theophylline toxicity? What is a therapeutic level?
- What is the preferred treatment for a new patient having asthma symptoms > 2 days/week, but not daily, and not more than 1x/day? What dose do you start?
- What is the preferred regimen for patients who are on medium-dose inhaled corticosteroids and still require albuterol daily?

Long-Term Control: Immunomodulators

Omalizumab (anti-IgE) is a monoclonal antibody that blocks the IgE receptors on mast cells and basophils. It is indicated in patients who have allergies and severe uncontrolled persistent asthma on high doses of an ICS + LABA (Steps 5–6 on asthma treatment algorithm, Table 3-4.)

Long-Term Control: Bronchial Thermoplasty

This technique was approved by the FDA in 2010. The bronchoscopic procedure delivers thermal energy to the airway wall, thereby reducing excessive airway smooth muscle. Benefits include improved asthma-related quality of life and reduced emergency room visits and hospitalizations.

Table 3-4: Treatment Steps Used in Asthma

	Preferred	Alternative
Step 1	SABA prn	N/A
Step 2	Low-dose ICS	Cromolyn, LTRA, nedocromil, or theophylline
Step 3	Low-dose ICS + LABA or Medium-dose ICS	Low-dose ICS plus either LTRA, theophylline, or zileuton
Step 4	Medium-dose ICS + LABA	Medium-dose ICS plus either LTRA, theophylline, or zileuton
Step 5	High-dose ICS + LABA and consider omalizumab for patients with allergies	N/A
Step 6	High-dose ICS + LABA + oral corticosteroid and consider omalizumab for patients with allergies	N/A

ICS = Inhaled corticosteroid; SABA & LABA = short- and long-acting beta2-agonists (inhaled); LTRA = leukotriene receptor antagonists

Management of Asthma

Notes on the Guidelines

Management discussion is based on the August 28, 2007 National Asthma Education and Prevention Program (NAEPP)'s Expert Panel Report 3:

Guidelines for the Diagnosis and Management of Asthma: <http://www.nhlbi.nih.gov/guidelines/asthma/index.htm>

Note the following several points made by these guidelines.

For chronic asthma management, think about asthma as 2 separate types of clinical encounters: **treatment initiation** and **continuing therapy** (rather intuitive). Refer to Table 3-3 during this discussion.

Treatment initiation occurs when a patient initially presents with signs/symptoms of asthma and is not on chronic management. Assess disease "severity" based on a number of factors (including the FEV₁, but not the peak flow!); then prescribe a Step level of treatment.

If your patient's risks include more than 1 category, then classify according to the most severe category. Use the purple part of the table to classify the patient, and find the patient's initial severity level by reading over into the green section of the table in the "Severity" column. The initial meds you start will be based on the initial severity classification and are designated as Steps 1–5 (see Table 3-3).

Continuing therapy. After instituting the proper initial Step level of treatment, reevaluate the patient again in 6 weeks to 2 months to assess the level of **control** using the same set of factors (now can use either FEV₁ or PEF).

At this initial follow-up visit and all future visits, determine the **control level** of asthma using the purple part of the table and reading over into the green section in the "Control" column to determine whether the asthma is well controlled, not well controlled, or very poorly controlled. Based on the level of control, modify Step level of treatment if needed (again, per Table 3-4).

Once the patient is well controlled for 3 months, look at the regimen required to maintain control, and assign the patient a category of severity that corresponds with that Step level of treatment (Table 3-5). Note that it is only at this point, when the patient is well controlled, that we can define how severe the disease is because the severity of asthma is based on the Steps needed to control it. The control aspect of care is dynamic: Every 3 months, step up

Table 3-5: Asthma Control Classification

Classification of Asthma Severity in Well-Controlled Patients				
On Step	Intermittent	Persistent		
		Mild	Moderate	Severe
1	2	3 or 4	5 or 6	

if the patient is not controlled or step down if controlled. The goal is to maintain control on the fewest medications.

So, initial assessment is based on “**severity** of presenting symptoms.” Determination of continuing therapy is based on “**control** of symptoms” with treatment. And determination of the “**severity of disease**” is based on how much medication is required to maintain good control of it. Be careful that you do not confuse these 2 uses of **severity**.

The Treatment Steps

Again, refer to Table 3-4 for this discussion.

Initial treatment of mild symptoms is with a SABA. Asthma is an inflammatory condition and anything more than very mild symptoms require **inhaled corticosteroids** be added in a **step-wise** approach starting with the lowest dose (Step 2). Note that before you increase the ICS dose from low to medium, it is preferred that you add a LABA (Step 3).

Chronic, severe asthma may require continuous oral prednisone. Steroid-sparing drugs have been tried, including methotrexate, cyclosporine, and troleandomycin, but the guidelines specifically state not to prescribe any of these drugs for the acute or long-term treatment of asthma.

When an exacerbation occurs, chronic management can be “stepped up” 1 or 2 levels, then slowly “stepped down” until symptoms recur, and then stepped up 1 level. When treatment is initially started, it is usually started 1 or 2 levels above the presumed severity level and then gradually stepped down in the same way.

Give chronic oral steroids **only** for severe asthma, and, even then, **repeat** attempts to wean off.

Use LABAs only for moderate-to-severe asthma and in addition to inhaled corticosteroids.

Treat **acute exacerbations** at any level the **same**: inhaled **SABAs** and oxygen as needed. Add OCS if the patient’s peak flow is $< 80\%$ after 3 treatments with inhaled SABA.

From all studies, guideline-based treatment of asthma is superior to other methods.

Management of Exercise-Induced Bronchospasm

Treat EIB with inhaled albuterol 15–30 minutes before exertion. A warm-up period prior to exercise is also helpful. Inhaled cromolyn is an alternative. Leukotriene modifiers are effective in $\sim 50\%$ of patients. LABAs also have some efficacy, but they should not be used if a drug is required for daily use.

Treat active bronchospasm with warm, moist air and inhaled short-acting beta2-agonists.

Management of Acute Exacerbations

Algorithms for managing acute asthma exist in the guidelines, and the one you use depends on whether you

are treating patients at their home or in the emergency department (ED). The algorithms are fairly lengthy and are taped to the wall of practically every ED in the U.S., so we won’t replicate them in full here. Important considerations include:

First, assess **severity** based on clinical history, exam (can be described to you over the phone), and peak expiratory flow (PEF; “peak flow”). Any PEF $< 80\%$ predicted or personal best suggests obstruction, and you should do something about it with meds.

If the patient is at home and responds to the SABA with a PEF $> 80\%$, then the patient can remain at home with increased frequency of a SABA—q 3–4 h.

If the PEF is $< 80\%$, give systemic steroids in whatever manner you can get them in the patient (IV if in respiratory failure).

If the patient is at **home** and has started oral steroids, keep tabs on the response to increased frequency of the SABA. Either the patient will stabilize or not. If a poor response is observed with PEF $< 50\%$ (either after the first round of SABA, or after trying OCS + SABA), the patient should come to the ED.

Patients with initial peak flow of $< 50\%$ should be told to get to the ED ASAP.

If the patient is presenting in the ED, and the PEF is $< 40\%$, the exacerbation is considered “**severe**.”

Institute 2 treatments of SABA, 20 minutes apart. Patients with a “severe” presentation should have ipratropium added to the SABA.

In the ED, the patient will be stratified into either a moderate (PEF 40–69%) or severe (PEF $< 40\%$) exacerbation based on response to the initial set of SABAs (+/- ipratropium).

Obviously, patients with impending respiratory failure at presentation fall out of the algorithm and into the ICU. Only patients with severe exacerbations continue to get ipratropium in the ED; moderate exacerbations can be treated with oxygen, OCS, and a SABA q hour.

A patient who has a sustained PEF $> 70\%$ 1 hour after the last SABA treatment and who “looks good” can be discharged to home with a prescription for continued outpatient SABA, OCS, and a close follow-up date.

A patient who sits in the ED receiving a SABA, oxygen prn, OCS, but maintains PEF 40–69% should be considered for hospitalization.

If the patient deteriorates in the ED, dropping the PEF $< 40\%$, admit them to the ICU.

Inpatient care consists of a SABA, oxygen prn, and systemic steroids. If the patient was on an ICS prior to exacerbation, continue the ICS during hospitalization.

Intubation and the Asthma Patient

During a severe asthma attack, the patient initially hyperventilates and $p\text{CO}_2$ will be low. As chest wall

Quick Quiz

- What is the preferred treatment for patients with exercise-induced bronchospasm?
- For an acute exacerbation, what peak flow measurement requires that you intervene with some medications?
- For an acute exacerbation, what peak flow measurement requires that you tell patients to go to the ED?
- For patients being treated in the ED for asthma, at what peak flow should you consider hospitalization?
- Explain permissive hypercapnia.
- What ventilator settings are appropriate for a patient intubated for a severe exacerbation of asthma?
- What is the specific definition of COPD?
- In COPD, what are the symptoms of disease in the large airways? The small airways? The alveoli?

and diaphragm muscles fatigue, he will start to breathe more and more slowly, normalizing the $p\text{CO}_2$ and finally becoming hypercapnic. Mild hypoxemia and hypocapnia are the norm with acute asthma attacks. **Normocapnia** or **hypercapnia** indicates impending respiratory failure and need for **intubation**!

If intubation is required, first sedate and then paralyze **only** if needed. Try to avoid use of neuromuscular blocking drugs to avoid prolonged blockade (might be harder to wean off). Avoid morphine because it may cause histamine release.

Auto-PEEP. Once intubated, do not bag too quickly! These patients require a prolonged expiration period, and ventilating at too high a rate causes progressive air trapping (“stacking,” “auto-PEEP”), which causes decreased venous return or barotrauma; e.g., tension pneumothorax. Decreased venous return → decreased filling pressure → decreased cardiac output, which subsequently → hypotension and poor perfusion of vital organs.

A very important method used when ventilating a patient with asthma is **permissive hypercapnia**—a technique of controlled hypoventilation. We no longer try to get the $p\text{CO}_2$ down to 40 to resolve the acute respiratory acidosis; this effort in just-intubated asthmatics has had bad outcomes (auto-PEEP)! Initially, focus on maintaining an O_2 sat of 90%, and don’t worry about the $p\text{CO}_2$ —a reasonable level is 60–70 (even 80) with a serum pH of 7.20–7.25.

Besides maintaining an adequate O_2 sat, you must ensure that the patient is getting all the air out! Listen with your stethoscope and check that the ventilator is not kicking in

while the patient is still exhaling, or check the flow over time waveform on the graphic package of the ventilator. Some ventilators will actually measure auto-PEEP during an expiratory hold maneuver.

Ventilator settings. When putting an asthmatic on a ventilator, use a **low rate**, **small tidal volume**, and **high flows**. Each of these addresses the need for a prolonged expiratory phase. **High flow** on the inspiration allows for less time devoted to inspiration and more to expiration. High flow may result in high pressure, but we are more concerned with end-inspiratory plateau pressure and avoidance of auto-PEEP.

COPD

Overview

Chronic obstructive pulmonary disease (COPD) is diagnosed when patients have typical symptoms indicative of disease of **large airways** (dyspnea, cough, and sputum production) with evidence of **irreversible** airway **obstruction** ($\text{FEV}_1/\text{FVC} < 0.70$) without another explanation for disease.

COPD results from chronic exposure to an inflammatory stimulus; e.g., cigarette smoke, pollution, dust. The lungs respond with inflammatory cell infiltrates and eventual development of structural changes due to repeated repair attempts. These structural changes are usually permanent, even after smoking cessation. Smoking causes damage to large airways, small airways, and in the lung parenchyma. In later stages, the pulmonary vasculature becomes involved when chronic hypoxic vasoconstriction causes pulmonary hypertension.

Although smoking is definitely a cause of COPD, not all cigarette smokers develop COPD—with disease expression definitely mediated by additional factors, such as genetics and environment.

Regarding general airflow obstruction, **2 hypotheses** exist that address the relationship between asthma and COPD.

- 1) The Dutch hypothesis says that asthma, chronic bronchitis, and emphysema are different expressions of 1 disease with expression determined by genetics and environment.
- 2) The British hypothesis says that asthma and COPD (chronic bronchitis and emphysema) are 2 separate diseases, with asthma being an allergic response and COPD being toxin (smoke) induced.

There is no consensus on which of these hypotheses is most correct.

Important Pathophysiology

Cigarette smoking damages big airways, little airways, and alveoli.

Large airway damage causes the cough and mucus production that we clinically diagnose as “**chronic bronchitis**.”

Small airway damage causes **airflow obstruction** with hyperinflation. Airflow obstruction is caused by narrowing of these small airways in response to the toxicity of the smoke. Inflammatory cells are recruited and infiltrate the walls, secreting mucus. Fibrosis ultimately contributes to chronic airflow obstruction and intermittent bronchoconstriction.

Over time, the smallest airways and alveolar spaces increase in size to try to overcome the airway resistance instigated by the narrowing—this phenomenon is called “**hyperinflation**.” As a compensatory maneuver, it works nicely, at first, and is expressed as a spirometric increase in Residual Volume. But as the lungs lose elastic recoil, the stretched-out small airways and alveolar sacs simply serve as traps for air, instead of forces to overcome resistance. Clinically, we see this as development of the barrel chest and prolonged expiratory phase, which is expressed as a spirometric increase in Total Lung Capacity.

Alveolar damage causes impaired gas exchange. Over time, the alveolar sacs become distended and perforated units, full of an inflammatory “soup” of macrophages and other immune cells. Pathologically, these changes are described as “emphysema.”

Emphysema can occur focally in the bronchioles (termed “centriacinar,” and seen most often in smokers—affecting upper lungs usually), or it can occur evenly across the lung (termed “panacinar,” and seen most often in α_1 antitrypsin deficiency—affecting lower lungs usually). Advanced COPD from cigarettes usually involves both types.

Disease of little airways and alveoli is present in almost all people with COPD, but the damage does not universally correlate with a specific presentation—meaning, the damage to these units causes symptoms that vary from person to person.

Diagnosis and Assessment of COPD

Suspect COPD in any patient who presents with complaints of dyspnea and productive cough—whether they smoke or not. Know that chronic bronchitis without objective airway obstruction is **not** COPD, by definition.

Recognize that patients sometimes will not describe dyspnea; rather, they will progressively restrict their exertion so that they are not performing activities that make them short of breath; e.g., used to take the stairs but now exclusively takes elevators, or gave up riding a bicycle.

Chronic bronchitis is defined as cough with sputum production for at least 3 consecutive months for at least 2 consecutive years. Patients may have a bronchospastic component responsive to bronchodilators.

Physical exam classically shows an obvious prolonged expiratory phase, wheezing, barrel chest, and increased lung sizes to percussion. Late-stage patients sit forward

on their elbows in the “tripod” position in order to harness strength from accessory muscles. These patients are often cyanotic in nail beds and lips.

The traditional definitions of “pink puffers” and “blue bloaters” have fallen out of favor because COPD is **always** a mixed pathologic picture of chronic bronchitis and emphysema. Differentiation between the 2 clinical presentations is artificial because the overwhelming majority of patients do not present that way.

Know: COPD, as an isolated disease process, does not cause clubbing. If you see clubbing in a patient with COPD, look for other lung pathology, such as idiopathic pulmonary fibrosis and lung cancer.

The Global Initiative for Obstructive Lung Disease (**GOLD**) is a worldwide association that sets criteria for the diagnosis, grading of severity, and management of COPD.

The GOLD criteria categorize COPD into 4 levels of severity based on the reduction of the FEV_1 compared to the predicted value. All 4 groups require spirometric diagnosis of irreversible obstruction as defined by an $FEV_1/FVC < 0.70$. The COPD levels are:

- GOLD 1 = Mild: $FEV_1 \geq 80\%$ predicted
- GOLD 2 = Moderate: FEV_1 50–79% predicted
- GOLD 3 = Severe: FEV_1 30–49% predicted
- GOLD 4 = Very severe: $FEV_1 < 30\%$ predicted

There is some controversy that GOLD spirometric diagnostic criteria over-diagnose COPD in the elderly and under-diagnose in patients younger than 45 years with mild disease.

The GOLD guidelines had a **major update** in 2011. This update emphasizes that spirometry alone does not capture COPD’s full impact on individual patients. Therefore, it is recommended to assess COPD by a combination of:

- the GOLD **spirometry** criteria (1–4) just discussed,
- severity of **symptoms** (using COPD Assessment Test [CAT] or Modified British Medical Research Council [mMRC]) breathlessness scale,
- risk of **exacerbations** (based on previously treated exacerbations), and
- the presence of **comorbidities**.

Based on this combined assessment, patients are divided into four groups:

- A = fewer symptoms, low risk of exacerbations
- B = more symptoms, low risk
- C = fewer symptoms, high risk
- D = more symptoms, high risk

Treatment recommendations are based on these A, B, C, and D patient groupings. The groups are associated with the GOLD spirometric classifications, such that group A and B patients tend to fall into GOLD 1–2 and groups

Quick Quiz

- What is the specific definition of “chronic bronchitis”?
- What is the significance of clubbing in a patient with COPD?
- What is the best prognostic indicator in COPD?

C and D fall into GOLD 3–4. See the GOLD Pocket Guide referenced in For Further Reading on [page 3-78](#) for additional information.

The treatment that we discuss below takes into account these recommendations.

The **BODE** index (**B**ody mass index, **O**bfusion, **D**yspnea, **E**xercise capacity) adds a little to the GOLD severity criteria by considering how outcomes are affected by some extrapulmonary manifestations. Patients get points for FEV₁, 6-minute walk test results, dyspnea, and body mass index. The result helps prognosticate 4-year survival and assess response to treatment changes. Higher BODE scores are associated with an increasing risk of death.

COPD pathology results in airflow obstruction, hyperinflation, and problems with gas exchange.

Must-know items and useful clinical pearls:

- The **best** prognostic indicator in COPD is FEV₁.
- The best predictor of FEV₁ is **pack years** of cigarette smoking. The normal age-related decrease in FEV₁ is ~15–30 mL/yr. COPD patients can lose 60–120 mL/yr of lung function.
- Cessation of smoking is most beneficial to the lungs when accomplished at a **younger** age and before any loss of pulmonary function.
- **P_aO₂** does not usually fall until late in the disease, when FEV₁ is **< 50%** of predicted (or even lower in many patients).
- Chronic **retention** of CO₂ does not usually occur until very late in the disease, when FEV₁ is **< 25%** of predicted.
- Cor pulmonale occurs only after prolonged, marked reductions in FEV₁ (usually **< 25%** predicted) with severe, chronic hypoxemia.
- Hypoxemia in COPD is almost exclusively due to V/Q mismatching; therefore, COPD exacerbations **are** responsive to oxygen. If a patient with an apparent COPD exacerbation is not responsive to moderate amounts of oxygen, consider another cause for decompensation, such as a shunt process.

One more time, review of lung mechanics in emphysema: Decreased elastic recoil means increased compliance (and increased TLC). Although there is an increase in

TLC, there is an even greater increase in residual volume from air trapping, so the VC (or FVC) is decreased! This air trapping leads to the process of dynamic hyperinflation and can result in a large amount of auto-PEEP (intrinsic PEEP). DLCO is reduced in patients who have a great amount of emphysema.

[Image 3-1](#) through [Image 3-3](#) show classic COPD changes on CT and chest x-rays.

Treatment of COPD

General Treatment Principles

Management based on 2007, 2009, 2011 GOLD updates:

- Educate everybody and encourage them to stop smoking. Nicotine replacement therapy in many forms (gum, nasal spray, patch, tablets, lozenges, inhaler) is effective. Pharmaceutical options include varenicline, bupropion, and nortriptyline.
- SABAs as needed in all patients.
- **LABAs** in moderate-to-very severe stages when SABAs fail to control symptoms. These drugs **reduce exacerbations** and **hospitalizations**. Tiotropium improves the efficacy of pulmonary rehab, if the patient is enrolled.
- **ICS** in patients with GOLD 3–4 disease. In these groups, these drugs reduce exacerbations but also improve lung function and quality of life. However, they are associated with an increased risk for pneumonia. Do not use as long-term monotherapy. The drugs should be combined with LABAs.
- Combination LABA + ICS is more effective at reducing exacerbations than either agent alone, but it also is associated with an increased risk of pneumonia.
- GOLD 3–4 patients may benefit from roflumilast, a phosphodiesterase-4 inhibitor.
- Reserve theophylline for those who are on maximum therapy. It adds a slight bronchodilator effect to salmeterol, which relieves breathlessness and reduces exacerbations.



Image 3-1: CT: Bullous emphysema

Courtesy of Vinay Malleshwar, MD

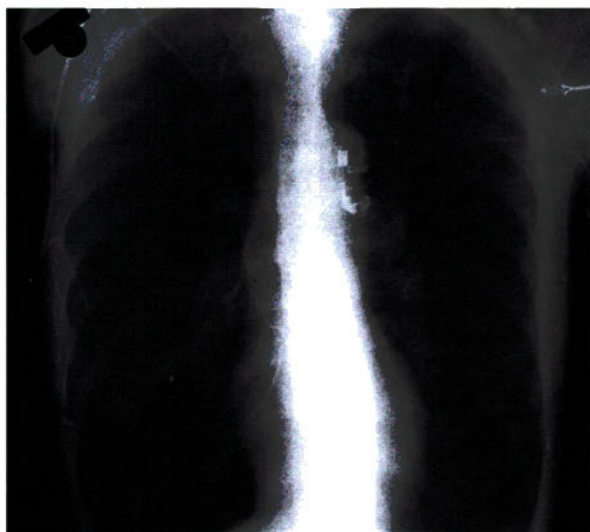


Image 3-2: Emphysematous COPD

- Do not use nedocromil or leukotriene modifiers. These are ineffective in COPD.
- Pneumococcal and influenza vaccines.
- Oxygen as needed when patients meet criteria (see below).
- Monitoring of blood gases in patients with $FEV_1 < 50\%$ predicted or clinical signs of respiratory or right heart failure.
- Screen for α_1 -antitrypsin deficiency in all Caucasian patients who get COPD and are younger than 45 years.

Oxygen therapy for patients with COPD:

The focus of O_2 therapy for patients with COPD (or any patient, for that matter) in respiratory distress is to give them enough O_2 to achieve 90% O_2 saturation—or as close as possible. This is a **required endpoint** in initial management! Not treating hypoxia causes further end-organ damage, worsening pulmonary vasoconstriction, and a downward spiral to death.

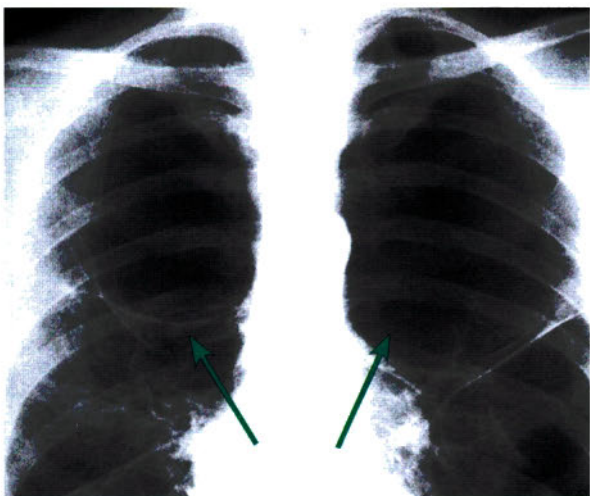


Image 3-3: Chest x-ray showing emphysema bubbles

Criteria for starting continuous O_2 :

- Resting $P_aO_2 \leq 55$, or
- O_2 sat (S_aO_2) $\leq 88\%$, or
- P_aO_2 55–60 mmHg, or S_aO_2 88%, with evidence of pulmonary hypertension, edema consistent with HF, or hematocrit $> 55\%$.

Continuous O_2 use, if needed per the above criteria, **increases** life span. Keep these patients on supplemental O_2 24 hr/d (if not possible, at least 15 hr/d).

Intermittent O_2 use: Some patients have similar findings of hypoxia/desaturation during low-level exercise or sleep. Give these patients supplemental O_2 during these activities; but if they meet the criteria above, the O_2 should be **continuous** x 24 hours.

Reevaluate patients placed on oxygen 2 months after they are on a stable regimen of drug therapy—oxygen can be discontinued in up to 40%!

Pulmonary Rehabilitation:

A pulmonary rehabilitation exercise regimen results in a small but significant improvement in overall strength and endurance. Know: pulmonary rehab improves symptoms and quality of life and reduces the hospitalizations and days in the hospital. The 2011 GOLD update states that survival is improved (level of evidence B).

Lung volume-reduction (LVR) surgery:

LVR surgery is useful for emphysematous patients with upper lobe disease and low exercise capacity. The Center for Medicaid and Medicare Services (CMS) now pays for LVR surgery when performed by an approved center as part of the NETT trial in patients who are symptomatic despite using bronchodilators and pulmonary rehabilitation. However, the most severe group is excluded from approval due to high mortality.

Know: **None** of the medications **prevent the decline of FEV_1** in COPD! The only interventions that affect COPD outcomes long-term are oxygen in hypoxemic patients, smoking cessation, lung volume reduction surgery, and lung transplantation in appropriately selected patients.

Treatment of Stable COPD

As discussed above, the GOLD COPD assessment classifies patients into groups A, B, C, and D (see [page 3-18](#)). Note: In the following treatment, **bronchodilator means either anticholinergic or beta-agonist**; e.g., short-acting bronchodilator can be either short-acting anticholinergic or SABA; long-acting bronchodilator can be either long-acting anticholinergic or a LABA.

Treatment, based on this classification:

- Group A patients: **short-acting bronchodilator** (short-acting anticholinergic **or** SABA) to improve

Quick Quiz

- Describe the emergent workup of a patient with an apparent COPD exacerbation.
- A COPD patient with evidence of right heart failure has a resting P_aO_2 of 58. How many hours a day should he be on supplemental oxygen?
- What are the benefits of pulmonary rehabilitation? Does pulmonary rehab improve mortality?
- A 30-year-old nonsmoker presents with COPD and emphysematous bullae in the bases. What disease should you suspect?
- What is the single environmental agent that worsens lung disease in all types of α_1 -antitrypsin deficiency?

breathlessness; alternative is combination of short-acting bronchodilators or use of single long-acting bronchodilator.

- Group **B** patients: **long-acting bronchodilator** (long-acting anticholinergic **or** LABA); for patients with persistent breathlessness, long-acting bronchodilators can be combined (anticholinergic + beta-agonist).
- Group **C** patients: First choice is combination therapy with **ICS + long-acting bronchodilator**. Alternatively, two long-acting bronchodilators can be combined. Short-acting bronchodilators can be combined with theophylline if long-acting bronchodilators are unaffordable; **roflumilast** can be used for patients with chronic bronchitis.
- Group **D** patients are initially treated same as group C with **ICS + long-acting bronchodilator**; alternatives include ICS + LABA + long-acting anticholinergic $\pm$ roflumilast if chronic bronchitis is present.

Treatment of Exacerbations of COPD

An exacerbation is a worsening of respiratory symptoms beyond the normal variation requiring a change in medication. For **assessment** of the exacerbation:

- Do a **chest x-ray** because up to 23% show new infiltrates that change the chosen therapy.
- Do an **ECG** and pay attention to the history for clues suggesting pulmonary embolism such as $S_1Q_3T_3$, new RBBB, or RAD. This is a hot topic now because of data showing that pulmonary emboli are often misdiagnosed as COPD exacerbations. Remember that the most common ECG finding in pulmonary embolism is sinus tachycardia.
- Assess the S_aO_2 and draw an **arterial blood gas** if respiratory failure is suspected. $P_aO_2 < 60$ mmHg or $S_aO_2 < 90\% \pm P_aCO_2 > 50$ mmHg on room air = respiratory failure. Give oxygen with close observation to keep the saturation $> 90\%$. Note that patients with initial abnormal blood gases are at risk for

hypercarbia and subsequent respiratory failure with supplemental O_2 administration.

- Do **not** use spirometry or peak flows to diagnose or assess the severity of an exacerbation.

For **treatment** of COPD exacerbation:

- Start treatment with **SABA** and add an anticholinergic drug if the patient doesn't improve quickly.
- Begin **systemic corticosteroids**. These drugs shorten recovery, reduce the risk of early relapse, and decrease the length of the hospital stay. 40 mg of oral prednisone is recommended for 10–14 days.
- In moderately and severely ill patients, the presence of purulent sputum is an indication for empiric antibiotics targeted against *Moraxella*, pneumococcus, and *Haemophilus influenzae*. GOLD 3 and 4 patients also are at risk for infection with *Pseudomonas*. Recommended antibiotics are broad in spectrum: amoxicillin-clavulanate, azithromycin, and respiratory quinolones. Antipseudomonal coverage is parenteral.
- NPPV (noninvasive positive-pressure ventilation) reduces hospital stay and improves mortality in exacerbations with impending respiratory failure.

α_1 -ANTITRYPSIN DEFICIENCY

Overview

α_1 -antitrypsin deficiency causes 1–2% of COPD cases, so it is **rare**. Consider it in **young** smokers with bullous COPD in the lung bases and/or family histories of both liver and lung disease.

The alleles responsible for α_1 -antitrypsin deficiency occur on a locus called *Pi*. The most common allele is *Pi M*. The *M* means it moves moderately fast on an electrophoretic strip. There are variants of *Pi M*—some move faster (*Pi F*) and some slower (*Pi Z*). Null alleles do not code for any α_1 -antitrypsin. Patients homozygous for the slower allele (*Pi^{ZZ}*) or heterozygotes for *Z* and null alleles (both groups referred to as *Pi^Z*) have severely decreased levels of α_1 -antitrypsin. Levels of α_1 -antitrypsin in heterozygotes (*Pi^{MZ}*) are about 60% of normal.

Disease is variable among all individuals with the deficiency. For example, some *Pi^Z* individuals do **not** get COPD; and, airflow obstruction among *Pi^{MZ}* individuals is unpredictable. Contrary to previous teachings, some COPD studies show that heterozygote (*Pi^{MZ}*) nonsmokers may have more airflow obstruction than patients with normal α_1 -antitrypsin levels (*Pi^{MM}*). One unifying factor in disease progression is cigarette smoking. Smoking worsens lung disease in both groups. Genetic factors, other than *Pi* locus alleles, likely account for the variability in disease expression.

Don't forget! Patients with α_1 -antitrypsin deficiency can also develop progressive **liver fibrosis** and **cirrhosis**. As with the lung disease, expression of the genetic defect in

the liver is variable, but Pi^Z patients are most affected. As with cirrhosis of any cause, there is an increased incidence of hepatoma.

Disease presents as airflow obstruction in a young person with unusual bullous formation in the lung bases, and/or elevated serum aminotransferase levels. In severe Pi^Z cases, liver disease can progress to cirrhosis in childhood.

Diagnose α_1 -antitrypsin deficiency by measuring the serum level of α_1 -antitrypsin and genetic testing of the Pi locus. 2009 and 2011 GOLD guidelines recommend screening with a serum level in any Caucasian patient who develops COPD and is < 45 years old or has a “strong” family history of COPD. The benefit in knowing phenotype and genotype is to better counsel not only the patient but also the patient’s family members.

Treatment of α_1 -Antitrypsin Deficiency

α_1 antiprotease (pooled human α_1 -antitrypsin) can be given in weekly IV infusions in patients with severe disease. It is expensive—on the order of \$40,000/year above the cost of COPD maintenance treatment.

Selection criteria for IV augmentation: Pi^Z status and serum α_1 -antitrypsin level < 11 $\mu\text{mol/L}$ (equal to 50–80 mg/dL depending on the assay) with both an abnormal chest CT and spirometry. Patient must be a nonsmoker or ex-smoker.

Even so, contrary to the selection criteria, some experts and the makers of the replacement product advocate treating all deficient individuals with low levels of α_1 -antitrypsin to help maintain normal lung function.

In addition to the IV infusion, patients should continue to be treated as before for COPD with bronchodilators, antibiotics as needed, and yearly vaccines. And don’t forget the vigorous anti-smoking message.

When the emphysema is severe, the only treatment is lung transplantation. Note that the IV infusion has no effect on the liver disease, and the only treatment for cirrhosis is also liver transplant.



Image 3-4: CT chest: Bronchiectasis

BRONCHIECTASIS

Bronchiectasis is persistent, pathologic dilatation of the bronchi caused by infection-mediated inflammation and destruction of airway walls. The bronchi fill with mucus and pus, and then become fibrotic. The infectious insult sometimes is primary (e.g., adenoviral infection), or it may be secondary, due to an underlying lung disease that prevents adequate clearance of organisms from the respiratory tree (e.g., cystic fibrosis).

Consider it in the older, middle-aged female with a chronic cough productive of purulent sputum (+/- hemoptysis) that either arose insidiously over years or followed a dramatic lung event (e.g., chemical inhalation or bad pneumonia).

Specific causes of bronchiectasis:

- Initial infections, such as severe viral pneumonia from adeno- or influenza virus; severe, untreated or poorly treated staph or gram-negative pneumonia; *Bordetella pertussis* infection; and tuberculosis (especially if focal area of involvement). It is often difficult to tell whether the organisms growing in the patient’s lungs initiated the bronchiectasis or are colonizing. *M. avium* complex is sometimes just a colonizer of bronchiectatic lungs, but it can also cause bronchiectasis.
- Focal lung obstructions as with endobronchial tumors, lymph nodes, or foreign bodies.
- Systemic diseases that reduce mucociliary clearance or prevent an adequate immune response and, thus, allow for colonization of destructive bacteria (e.g., cystic fibrosis, ciliary dyskinesia, HIV/AIDS, and immunoglobulin deficiency).
- Inhalation of a toxin (e.g., chemical fumes or gastric contents).
- Allergic bronchopulmonary aspergillosis (ABPA).
- α_1 -antitrypsin deficiency (rare).

Diagnose bronchiectasis with a HRCT of the chest (Image 3-4). Chest x-rays are nonspecific. Routine Gram stains with culture and AFB smears/cultures should be done to assist treatment decisions. Based on other clinical history and physical exam, you might consider testing for HIV, measuring immunoglobulins, performing the prick test for ABPA, and/or ordering a sweat chloride measurement.

Treatment is a 10–14-day course of antibiotics to reduce the burden of pathogenic organisms in the small airways. (Or, treat ABPA if that is the underlying cause.)

The antibiotic decision should be driven by microbiologic data from sputum. The big organism to worry about is *Pseudomonas*; in CF patients, it is often multi-drug resistant. Treat based on resistance testing; but empirically, start with an oral ciprofloxacin or aminoglycoside plus a parenteral antipseudomonal penicillin.

Quick Quiz

- What disease should you suspect in a patient with a chronic cough productive of necrotic-appearing sputum?
- What are the newer treatments for cystic fibrosis?
- Name the common clinical features of all interstitial lung diseases.

No solid data exist on benefit of chest physiotherapy and mucolytics, but they are often used. Chronic prophylaxis for bronchiectasis does not prevent acute infection or deterioration of pulmonary function and breeds resistant bacteria.

Do not treat bronchiectasis with aerosolized recombinant DNase (because it can cause harm), except in patients who have underlying cystic fibrosis.

Massive hemoptysis or unresolving focal infections usually go for surgical resection.

CYSTIC FIBROSIS

Cystic fibrosis (CF) occurs as a result of a mutation in the CF transmembrane conductance regulator protein (CFTR) gene on chromosome 7. This protein normally controls Na^+/Cl^- transport on epithelial membranes in the lung, GI tract, sweat glands, and urogenital system. The gene mutation results in decreased Na^+ absorption and Cl^- secretion. Lung mucus is dehydrated, sticky, and low in oxygen, which contributes to bacterial superinfection with particularly bad, and difficult to treat, organisms.

5% of patients with CF initially present in adulthood, and median survival is now 41 years.

Initial diagnosis: Consider adult CF in a patient with a history of recurrent sinusitis, nasal polyps (found in 25%), weight loss, and a chronic cough productive of thick, purulent sputum with recurrent exacerbations of febrile respiratory infections requiring antibiotics. Sputum Gram stain showing gram-negative rods (GNRs) and cultures that grow staph, *H. influenzae*, *Pseudomonas*, enteric GNRs (*Proteus*, *E. coli*, *Klebsiella*), and weird organisms that you've never heard of before (e.g., *Alcaligenes xylosoxidans* and *Burkholderia gladioli* or *B. cepacia*) should really tip you off. *Aspergillus* and non-tuberculous mycobacteria are also commonly found.

Most male patients with CF are infertile, so that may be an additional historical clue.

Clubbing and signs/symptoms of cor pulmonale occur in late-stage disease.

Chest x-ray changes are nonspecific (hyperinflation and bronchial cuffing). Pneumothorax occurs in 10%.

Spirometry shows reductions in FVC and $\text{FEV}_{1\text{L}}$, some of which is reversible until late disease.

Screen for CF by demonstrating elevated concentrations of chloride in sweat. 1–2% of patients with CF have normal sweat chloride tests, so continue testing if the patient has a strong clinical history but a negative sweat chloride test. The nasal potential difference (NPD) test and a genetic analysis are confirmatory tests.

Manage CF with aggressive pulmonary toilet (percussion and exercises, as these maneuvers preserve lung function), pancreatic enzymes, supplemental vitamins A, D, E, K, and culture-guided antibiotics for exacerbations.

Recombinant human DNase and inhaled hypertonic saline are 2 recent additions to CF management. DNase degrades accumulated DNA in the airways and provides for better airflow. Hypertonic saline is acceptable to improve airway clearance.

IV antibiotics are used for more severe exacerbations or resistant organisms. All gram-negative organisms get 2 antipseudomonal antibiotics until you know resistance patterns and identification of your organism.

For chronic management of CF, antibiotic prophylaxis using rotations of drugs helps prevent exacerbations by reducing microbial colonization. Inhaled aminoglycosides, or aztreonam, and oral azithromycin are commonly used.

Bilateral lung transplantation is an end-stage treatment option with a 65% 5-year survival rate.

Complications of CF include: respiratory failure, pulmonary hypertension with cor pulmonale, pneumothorax, and hemoptysis.

INTERSTITIAL LUNG DISEASES

OVERVIEW

Interstitial lung diseases (ILDs) are a diverse (> 100!) group of disorders that affect the supporting tissue of the lung, especially structural portions of the alveolar walls.

The name is partly a misnomer because there is often bronchial and alveolar involvement. Some call it diffuse parenchymal lung disease (DPLD)—which is more correct. However, we call it ILD in this discussion.

The interstitium usually is just a potential space between the capillaries and the alveoli. With ILDs, there is early alveolar disease with later collagen deposition in the interstitium, which causes scarring and changes the architecture of the alveoli and airways.

ILDs have **common** factors in their clinical presentation: dyspnea, diffuse disease on x-ray, restrictive PFTs with decreased DLCO, and an elevated A-a gradient (Image 3-5 and Image 3-6).

ILDs most easily can be grouped into those of **known** cause and those that are **idiopathic**. Those of known cause are usually due to **dust** (organic or inorganic) from occupational or environmental exposures. We discuss these groups of ILDs as follows:

- 1) Occupational and environmental causes of ILD
- 2) Idiopathic interstitial pneumonias (IIP)
- 3) Other causes of ILD

ILDs: OCCUPATIONAL AND ENVIRONMENTAL

Overview

There are 3 categories of occupational/environmental ILDs:

- 1) Hypersensitivity pneumonitis
- 2) Organic dust induced: byssinosis
- 3) Inorganic dust induced: asbestosis, silicosis, coal workers' pneumoconiosis, and berylliosis

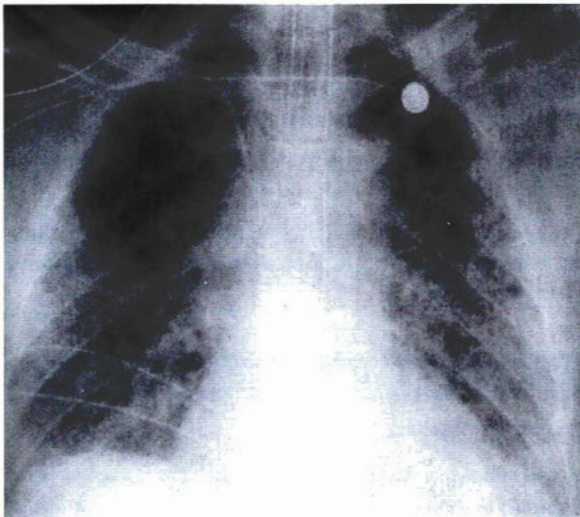


Image 3-5: PA chest: diffuse interstitial fibrosis

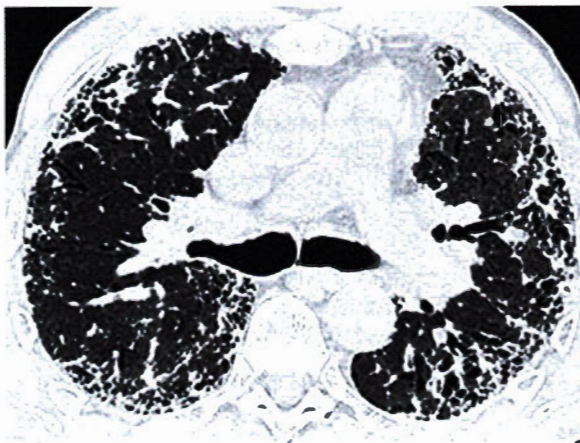


Image 3-6: Chest CT: pulmonary fibrosis

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an **immune-mediated** granulomatous reaction to organic antigens. As such, not many people get it—just those susceptible to it.

Poorly formed granulomas are typical. (The granulomas in sarcoidosis are much denser.)

It has a wide range of causes, and the occupation of the patient, solicited during the history-taking, often tells you the cause. These include:

- Moldy hay (thermophilic actinomycetes), aka “farmer’s lung”
- Pet birds, aka “bird-fancier lung” or “bird-breeder lung”
- Grain dust (workers in a grain elevator)
- Isocyanates
- Air conditioning systems
- Crack cocaine

Hypersensitivity pneumonitis has acute, subacute, and chronic forms and a typically insidious onset. Think about it in a patient with “recurrent or persistent pneumonias” who gives you a history of exposure to 1 of the above.

Diagnose by **history**. Chest x-ray may reveal recurrent infiltrates, but these are **fleeting**. Serum precipitins are **nonspecific** for hypersensitivity pneumonitis because these indicate only exposure, and most people exposed to these antigens have no immune reaction.

Differential diagnosis includes other causes of “recurrent or persistent pneumonias”: **eosinophilic pneumonia** and cryptogenic organizing pneumonia (COP = idiopathic form of organizing pneumonia, previously idiopathic BOOP). Hypersensitivity pneumonitis also may be confused with sarcoidosis. Note that BAL shows an increased number of lymphocytes, with a helper/suppressor ratio of < 1 (sarcoidosis has a ratio of $> 4:1$).

Best treatment is to **remove** the patient from the offending antigen. Corticosteroids are beneficial in acute disease.

Organic Dusts that Cause ILD: Byssinosis

Byssinosis is caused by inhalation of cotton, flax, or hemp dust. Not immune-related, so no sensitization needed. Early stage has occasional chest tightness; late stage has regular chest tightness toward the end of the 1st day of the workweek (“Monday chest tightness”). The frequency of symptoms slowly increases to include more days.

Inorganic Dusts that Cause ILD

Overview

These ILDs are: asbestosis, silicosis, coal workers' pneumoconiosis, and berylliosis.

Quick Quiz

- What disease do you think of when a patient presents with recurrent pneumonia each time she changes her bird cage?
- Characterize the x-ray abnormalities in patients with a history of significant asbestos exposure.
- Smoking + asbestosis increase the risk of what types of lung cancer?

Asbestos

Asbestos exposure (not asbestosis) causes bilateral, mid-thoracic pleural thickening, plaques, and calcification. The pleural thickening usually involves the mid-thorax (posterolateral) and spares both the costophrenic angles and the apices. Remember that pleural plaques and pleural thickening are completely benign; they are **not** manifestations of **asbestosis** (Image 3-7).

The most common manifestation of asbestos exposure in the first 10 years is benign asbestos pleural effusions (**BAPE**). These vary from serous to bloody and tend to occur early in the exposure history (within 5 years). 1/3 of patients have eosinophils in the pleural fluid.

Malignant mesotheliomas are associated (80%) with asbestos exposure (again, merely exposure—not necessarily asbestosis!) It is a tumor arising from the mesothelial cell of the pleura—the area affected by asbestos exposure. Latency period can be > 40 years. It is **not** associated with smoking. It is usually a rapidly fatal disease.

Asbestosis is the pulmonary disease—the parenchymal fibrosis and resultant impairment—caused by prolonged

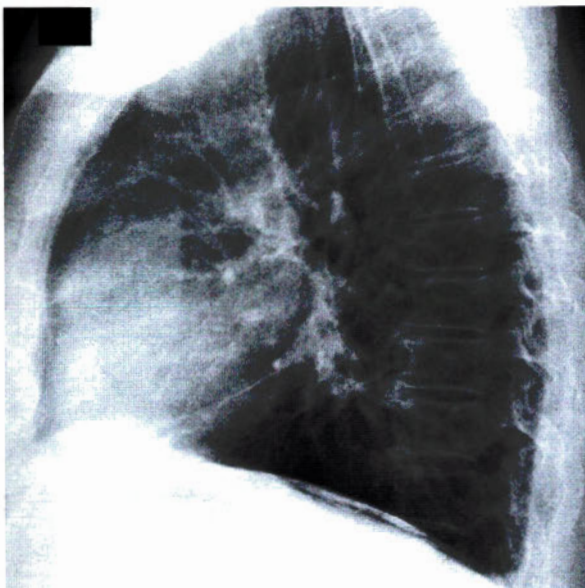


Image 3-7: PA Lateral Chest: asbestos pleural plaques

exposure to asbestos. The pulmonary parenchymal fibrosis develops mostly in the bases. Asbestosis generally occurs with > 10 years of moderate exposure, although the latency period is > 30 years! Smoking has a synergistic effect with asbestosis in the development of lung cancer. The associated lung cancers are **squamous** and **adeno**—but **not** small- or large-cell!

There is no specific treatment for asbestosis.

Silica

Silicosis is the most prevalent occupational disease in the world. It requires years of exposure to crystalline silica to develop—as in mining, glassmaking, ceramics, sand-blasting, foundries, and brick yards—with a latency of 20–30 years.

Silica ingested by alveolar macrophages renders them ineffective—so a +PPD in these patients makes the diagnosis of latent tuberculosis infection (LTBI), and these patients should be treated with anti-tuberculous drugs per the ATS guidelines, regardless of age. All patients with silicosis have an increased risk for the development of TB and malignancy, so consider screening for these conditions.

Simple nodular silicosis (i.e., small nodules) is “fibro-calcific” and usually involves the **upper lung**, so the differential diagnosis includes TB, coal workers’ pneumoconiosis, and berylliosis. Silicosis is associated with these **silicotic nodules**, involvement of the **hilar** lymph nodes (“hilar eggshell calcification”), and increased susceptibility to **TB**. Silica is now considered a human carcinogen. See Image 3-8 and Image 3-9.

There is no specific treatment for silicosis, but if symptoms rapidly worsen, think TB.

Complicated, nodular silicosis (i.e., big nodules; also called progressive, massive fibrosis) has nodules > 1 cm, which tend to coalesce.

Silicoproteinosis. Overwhelming exposure leads to silicoproteinosis in ~ 5 years, which results in alveolar filling with eosinophilic material similar to that found in pulmonary alveolar proteinosis (page 3-32). These patients present with symptoms easily mistaken for pulmonary edema.

Corticosteroids are thought to be beneficial in acute silicosis, but not in chronic disease.

Consider lung transplant for those with severe disease.

Note: Asbestosis involves the **lower** lung while silicosis involves the **upper** lung.

Coal

Coal workers’ pneumoconiosis (CWP) also has simple and progressive forms. The chest x-ray shows **upper lung** field nodules (similar to silicosis and berylliosis). Progression of simple CWP correlates with the amount of coal dust deposited in the lungs, whereas

complicated CWP does not. Complicated CWP is a progressive massive fibrosis defined by nodules > 2 cm with no hilar involvement. With large depositions of coal dust, patients have melanoptysis. As expected, cigarette smoking accelerates the deterioration of pulmonary function. No association with TB. No specific treatment.

Caplan syndrome is seropositive rheumatoid arthritis associated with massive CWP. This syndrome is heralded by the development of peripheral lung nodules (in addition to the upper-lung field nodules seen in CWP).

Beryllium

Berylliosis (or chronic beryllium disease; CBD) is caused by a cell-mediated immune response that can occur from ≥ 2 -year exposure to even slight amounts of beryllium. Especially suspect in persons working in high-tech electronics, alloys, ceramics, the Manhattan Project nuclear program, and pre-1950 fluorescent light manufacturing.

It usually causes a **chronic interstitial pneumonitis**, which tends to affect the **upper lobes** (like silicosis, TB, and CWP). Patients often have hilar lymphadenopathy that **looks identical** on chest x-ray to that caused by **sarcoidosis**.

Diagnosis of CBD:

- History of beryllium exposure
- Positive beryllium lymphocyte transformation test (BeLPT)
- Lung biopsy result showing interstitial cell infiltrates (with mononuclear cells) and/or noncaseating granulomas

This one can be treated! Corticosteroids are very effective. Methotrexate (MTX) if no response or unable to tolerate corticosteroids.

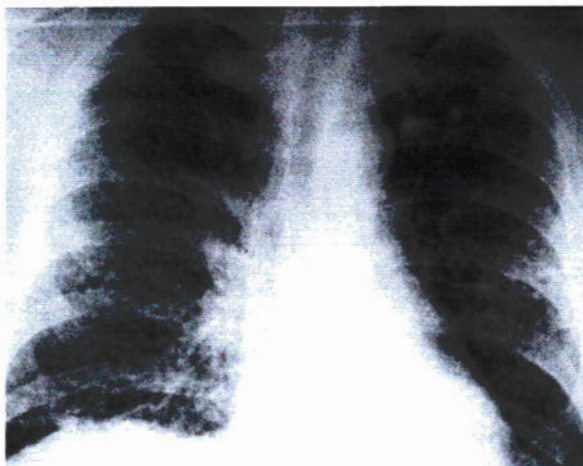


Image 3-8: PA chest: Simple nodular silicosis

ILDs: IDIOPATHIC INTERSTITIAL PNEUMONIAS (IIPs)

Overview

We will now discuss the second category of ILDs—**idiopathic** interstitial pneumonias (IIPs). Here is a listing in order of occurrence:

- Idiopathic pulmonary fibrosis (IPF; with usual interstitial pneumonitis [UIP] as the prototype)
- Nonspecific interstitial pneumonia (NSIP)
- Cryptogenic organizing pneumonia (COP, idiopathic form of organizing pneumonia; previously idiopathic BOOP)
- Acute interstitial pneumonia (AIP)
- Respiratory bronchiolitis-associated ILD (RB-ILD)
- Desquamative interstitial pneumonia (DIP)
- Lymphocytic interstitial pneumonia (LIP)

Each of these entities has specific histopathologic findings; IPF also has typical clinical and radiologic findings. We will discuss **2** of the most prominent IIPs: **IPF** and **COP**.

Idiopathic Pulmonary Fibrosis (IPF)

As its name implies, the etiology of idiopathic pulmonary fibrosis (IPF) is uncertain, although it is thought to be autoimmune. IPF is a diagnosis of exclusion. It accounts for up to 50% of ILDs.

There are **limited extrapulmonary** manifestations of this disease, although clubbing may be seen in 50–60% of patients.

M = F, average age = **55 years**, but it occurs in all age groups.

Smoking exacerbates the disease.

About 10% of patients may have low titers of ANA or RF.

IPF, by definition, has the specific histopathologic findings of usual interstitial pneumonia (UIP).



Image 3-9: PA chest: Eggshell hilar calcifications in silicosis

Courtesy of Ying Maleshvarni, MD

Quick Quiz

- What type of CT scan assists with diagnosis of IPF? What findings are seen with this in early IPF?
- What is the typical presentation of a patient with IPF?
- What is the best test to document improvement of treated patients with IPF?

IPF ranges from an early inflammatory stage, amenable to treatment, to an untreatable late fibrotic stage with severe restrictive disease, pulmonary hypertension, and cor pulmonale.

Early IPF is characterized by “leakiness” of the capillaries and alveolar wall (from damage to the capillary endothelial cells and the adjacent Type I alveolar epithelial cells) → which causes interstitial and alveolar edema → which ultimately causes intraalveolar hyaline membrane formation.

The fluid in the alveoli and in the interstitial edema has increased numbers of alveolar macrophages. These release cytokines and pro-inflammatory mediators (tumor necrosis factor [TNF], interleukin 8, and leukotriene B₄)—some of which attract neutrophils. This is reflected in bronchoalveolar lavage (BAL) results of increased macrophages, neutrophils (PMNs = 20%), and eosinophils (2–4%). HRCT in early IPF shows a “ground-glass” pattern.

Late IPF leads to increasing alveolar-capillary permeability, desquamation of the alveolar wall, and fibrosis. Chest x-ray and HRCT show fibrosis with a **honeycomb** pattern.

Presentation: Consider IPF in a patient who presents with dyspnea, cough, dry mid-inspiratory “Velcro” crackles, and a diffuse interstitial process on chest x-ray.

Velcro crackles are loud and coarse. The crackles are mimicked when a Velcro patch is opened. These crackles are different from the sounds of fine crackles that can be mimicked when hair is rubbed together.

Clubbing is common. See [Table 3-6](#).

The chest x-ray changes correlate poorly with disease activity but generally show diffuse reticular or reticulonodular disease.

Like many ILDs, PFTs show a “restrictive intrathoracic” disease (low TLC, normal FEV₁/FVC, low DLCO). Know that, in IPF, a low DLCO correlates with the presence of pulmonary arterial hypertension (and thus, poor prognosis).

Diagnostic workup of IPF includes: Chest x-ray, HRCT (demonstrates “ground-glass” appearance in 1/3 of patients with true fibrosis), PFTs, ABG, and a functional

assessment and oxygen requirements with exercise (e.g. 6-minute walk test).

When the diagnosis is in question because of an **atypical presentation**, perform lung biopsy to characterize the pathology of the x-ray abnormalities and to exclude cancer/infections/vasculitis—especially since empiric treatment of IPF with immunomodulators can cause serious harm in these conditions, if misdiagnosed. Remember that UIP histology is consistent with IPF, although most diagnoses are now made with HRCT.

Definitely avoid lung biopsy if the patient has a negative environmental and drug history, is > 70 years of age, and has clubbing, coarse crackles, and honeycombed lungs. The latter findings suggest advanced disease that will not be modifiable by immunomodulators, and risk associated with treatment will outweigh benefit.

Treatment: IPF progresses steadily to death without treatment. With treatment, corticosteroids +/- either cyclophosphamide or azathioprine, ~ 20–30% of patients show **some** improvement. These are usually the patients with early IPF, in which there is a suppressible inflammatory component. Trials are ongoing to determine effective pharmacologic therapies for pulmonary artery hypertension complicating IPF.

The **best** tests for determining improvement in IPF is measurement of lung function, including lung volumes, DLCO, and ABGs with calculation of exercise-related A-a gradient. An objective response to corticosteroids, using these tests, is the best prognostic indicator available.

Cor pulmonale is treated symptomatically. Single-lung transplantation is an option for some late-IPF patients. Give IPF patients **pneumococcal** and **influenza** vaccines.

Organizing Pneumonia

Causes of Organizing Pneumonias

There are various types of organizing pneumonia that have the common finding of a chronic alveolitis.

50% of organizing pneumonia cases are idiopathic. The other 50% of cases are caused by/associated with the following:

- Inhalation of toxic fumes (e.g., smoke, paint aerosols, nylon flock fibers)
- Exposure to drugs (e.g., amiodarone, bleomycin, carbamazepine, minocycline, nitrofurantoin, phenytoin, penicillamine, sulfasalazine)

Table 3-6: Occurrence of Clubbing

Clubbing is almost always seen with:	Clubbing is commonly seen with:	Clubbing is almost never seen with:
Advanced IPF Asbestosis	Cystic fibrosis Bronchiectasis Lung cancer	Emphysema Sarcoidosis

- Immunodeficiencies
- Lots of infections (e.g., respiratory viruses, *Mycoplasma*, *Pneumocystis*, GNRs)
- Connective tissue disorders (e.g., rheumatoid arthritis)
- Myelodysplasia
- Radiation

Cryptogenic Organizing Pneumonia (COP)

Cryptogenic organizing pneumonia (COP = idiopathic form of organizing pneumonia; previously idiopathic bronchiolitis obliterans organizing pneumonia [BOOP]) is a very specific entity with an unknown cause. COP is a **bronchiolitis** (inflammation of the small airways) and a chronic **alveolitis** (the organizing pneumonia). The bronchiolitis causes a proliferation of granulation tissue within the small airways and alveolar ducts.

Consider COP in a patient with an insidious onset (weeks to 1–2 months) of cough, fever, dyspnea, malaise, and myalgias, possibly with 1 of the above risk factors. Often, patients have had multiple courses of antibiotics without effect. Rales are common. Chest x-ray shows some interstitial disease, bronchial thickening, and patchy bilateral alveolar infiltrate. Pulmonary function testing demonstrates a restrictive pattern with a reduced diffusion capacity.

You must differentiate COP from IPF because, contrary to IPF, COP has a **good** prognosis and responds to steroids. To differentiate IPF from COP, know that IPF is **even more** insidious in onset (> 6 months), and the patients do **not** have fever (Table 3-7). Lung biopsy is the definitive means of diagnosing COP.

Corticosteroids are the **treatment of choice** for COP. COP does not respond to antibiotics. **Slowly** taper corticosteroids over ~ 6–12 months since exacerbations can occur with tapering that is too rapid. Corticosteroid-sparing treatment can be used—typically cyclophosphamide.

OTHER CAUSES OF ILD

Overview

Other causes of ILD and diffuse lung disease are:

- Collagen-vascular diseases
- Sarcoidosis
- Eosinophilic granuloma

Table 3-7: Comparison of COP/BOOP and IPF

	COP/BOOP	IPF
Signs	Acutely ill appearing; Fever	Not acutely ill No fever
Onset of symptoms	Days to weeks	Very slow— at least 6 months
Chest x-ray	Patchy infiltrates	Diffuse infiltrates

- Lymphangiomyomatosis
- Vasculitides causing ILD: granulomatosis with polyangiitis, lymphomatoid, Churg-Strauss, bronchocentric, and PAN
- Eosinophilic ILDs: eosinophilic pneumonia, ABPA
- Alveolar proteinosis
- Idiopathic pulmonary hemosiderosis
- Goodpasture syndrome

Collagen Vascular Diseases and ILD

Rheumatoid arthritis. More than 1/3 of patients with RA get ILD! The most common lung problem in RA is pleurisy (with or without pleural effusion). Pleural effusions are **exudative** and can have uniquely very **low** glucose level with pseudochylous findings. (See Pleural Effusions on page 3-41.) Occasionally, these patients have **necrobiotic nodules**—usually in the **upper** lung zones. ILD can also be due to a complication of gold and methotrexate treatment in the RA patients, while COP may rarely result from penicillamine treatment.

SLE also causes painful pleuritis +/- effusion but additionally causes diffuse atelectasis and sometimes diaphragmatic weakness—and therefore orthopneic dyspnea that is **out of proportion** to the chest x-ray findings, although the x-ray may show elevated diaphragms. SLE also occasionally causes hemoptysis similar to that in idiopathic pulmonary hemosiderosis. SLE affects both lung and pleura more frequently than any other collagen vascular disease (60%), while systemic sclerosis (scleroderma) affects the lung alone more than any other. (100%! But no pleural changes.)

Systemic sclerosis (scleroderma) has 2 major lung effects:

- 1) Interstitial fibrosis
- 2) Intimal proliferation

It is this intimal proliferation in the pulmonary artery that causes pulmonary hypertension **out of proportion** to the pulmonary disease. So, it is not the ILD but the intimal proliferation that causes the real pulmonary problem in systemic sclerosis patients. Isolated pulmonary hypertension (**without** interstitial lung disease) occurs more often in patients with limited cutaneous sclerosis (previously “CREST syndrome”) than in patients with diffuse systemic sclerosis. Patients with systemic sclerosis are more susceptible to pneumonia. Chronic aspiration and gastroesophageal reflux are common and may have some relationship to the development of pulmonary fibrosis.

Both RA and systemic sclerosis are associated with exposure to silica, and both have an increased incidence of bronchogenic carcinoma!

Sjögren’s causes desiccation of the airways and is also associated with lymphocytic interstitial pneumonia (LIP).

Quick Quiz

- Characterize the differences in presentation between IPF and cryptogenic organizing pneumonia (COP).
- What finding in a pleural effusion may be helpful in distinguishing rheumatoid arthritis as an etiology?
- In what pulmonary disease is pulmonary hypertension out of proportion to the amount of pulmonary disease? What causes this?
- What PFTs results are associated with sarcoidosis?

Sarcoidosis

Sarcoidosis: “**Noncaseating granuloma**” is a multisystem disease. Chest x-ray findings are variable. Usually, there is bilateral hilar and/or mediastinal adenopathy +/- reticulonodular or alveolar infiltrates. PFTs may either be normal or show **restrictive** +/- **obstructive** mechanics. The radiographic staging of sarcoidosis (Table 3-8) illustrates the interesting point that hilar adenopathy disappears as the disease progresses (Image 3-10 and Image 3-11).

Serum angiotensin-converting enzyme level (ACE) is **nonspecific** and considered of **no use** in diagnosis, but it **may** be useful for monitoring progression of disease (controversial). If it was previously elevated when the disease was active, and low when inactive, serum ACE levels may be useful in determining if the disease is once again active. Hypercalcemia, hypercalciuria, and hypergammaglobulinemia are prevalent.

Sarcoidosis is a diagnosis of exclusion. A positive BAL shows an increased number of lymphocytes, with a helper/suppressor ratio of > 4:1 (hypersensitivity pneumonitis has a ratio of < 1). It is **imperative** to exclude the other granulomatous diseases, including hypersensitivity pneumonitis, berylliosis, and infectious diseases caused by mycobacteria and fungi. Material for histological exam should be cultured and examined for organisms.

While ensuring no organisms are present and cultures are negative, fiberoptic bronchoscopy with transbronchial or

bronchial wall biopsies showing **noncaseating granulomas** is the best method for diagnosis of sarcoidosis.

Erythema nodosum is an associated skin lesion that denotes a **good prognosis**! This form of sarcoidosis is called Löfgren syndrome.

Treatment: Overall, 75% of sarcoid patients recover without treatment. It rarely progresses to pulmonary fibrosis or pulmonary hypertension. Treat severe disease with **corticosteroids**, for lack of anything better. There is no set regimen. Corticosteroids **have not been proven to induce remissions** in sarcoidosis, although they do decrease the symptoms, and PFTs improve. Inhaled corticosteroids decrease the respiratory symptoms and may be used instead of systemic corticosteroids if the disease is primarily in the bronchi.

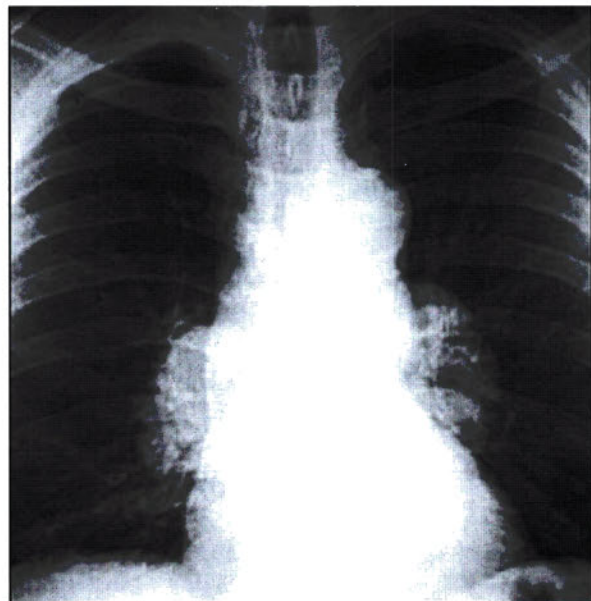


Image 3-10: PA chest: Stage I sarcoidosis

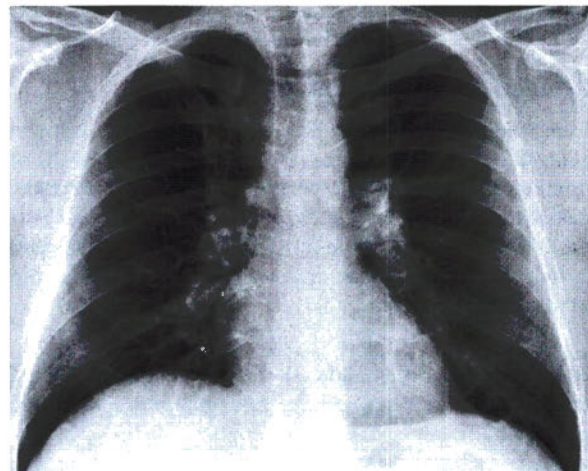


Image 3-11: PA chest: Stage II sarcoidosis

Table 3-8: Sarcoidosis Staging

Stage	Chest X-ray Findings
0	Clear
I	Bilateral hilar adenopathy
II	Adenopathy + parenchymal infiltrates
III	Diffuse parenchymal infiltrates
IV	Fibrosis, bullae, cavities

Indication for systemic corticosteroids is evidence of involvement of other organs:

- Eyes (conjunctivitis, uveitis)
- Heart (conduction abnormalities)
- CNS (signs of optic nerve or optic chiasm involvement)
- Lungs (severe pulmonary symptoms)
- Skin (severe skin lesions)
- Persistent hypercalcemia

Other medications available include hydroxychloroquine (Plaquenil®), infliximab (Remicade®), methotrexate, and thalidomide.

Eosinophilic Granuloma

Eosinophilic granuloma (also called Langerhans cell granulomatosis; previously called histiocytosis X). Virtually all affected patients are **smokers** and M > F. Langerhans cells are the predominant cell form. Patients have an interstitial disease with normal or **increased** lung volume (most ILDs have decreased lung volume). The granulomas can cause **lytic** bone lesions. It sometimes involves the posterior pituitary—leading to **diabetes insipidus**. In the lung, it causes interstitial changes and small cystic spaces in the upper lung fields, both of which are visible on chest x-ray, giving a **honeycomb** appearance (as seen with other fibrotic ILDs). Eosinophilic granulomatosis causing the combination of lytic bone lesions, diabetes insipidus, and exophthalmus is called **Hand-Schüller-Christian** syndrome.

10% of patients initially present with a **pneumothorax**, and up to 50% of these patients get a pneumothorax sometime in the course of their illness.

Diagnose by finding Langerhans cells on lung biopsy or BAL.

Treatment of eosinophilic granuloma: Stop smoking! Many do a trial of steroids, although drugs generally do not help. Occasionally, there is spontaneous resolution.

Again: Eosinophilic granuloma = pneumothorax, smoking.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) occurs almost exclusively in premenopausal women. It is the result of immature smooth muscle proliferation in the lymphatic, vascular, and alveolar wall/peribronchial structures. This proliferation results in the formation of constrictions and cysts in these structures. There is a genetic relationship to tuberous sclerosis.

Chest x-ray in LAM typically shows **honeycombing** (small cystic spaces) spread **diffusely** throughout the lung (in contrast to upper lung fields seen in eosinophilic granuloma above).

Thoracic and abdominal lymphatics are often involved, resulting in **chylous** pleural effusions—with

triglycerides > 110 mg/dL +/- chylomicrons in the fluid. Pneumothorax may occur.

Oophorectomy with progestin treatment is often recommended. Lung transplantation may be done, but the process may recur in the transplanted lung.

Again: LAM = premenopausal, pneumothorax, chylous effusion (TG > 110 +/- chylomicrons), and is associated with tuberous sclerosis.

Vasculitides that Cause ILD

Granulomatosis with Polyangiitis (GPA)

Previously termed “Wegener granulomatosis,” GPA is a vasculitis that involves all of the following:

- Affects the upper respiratory tract and paranasal sinuses
- Causes a **granulomatous** pulmonary vasculitis with large (sometimes cavitory) nodules
- Causes a necrotizing glomerulonephritis

Sometimes, it is limited just to the lungs (called “limited” GPA).

The ANCA test (antineutrophil cytoplasmic antibody—thought to be a destructive autoantibody) is often used as an adjunctive test. It is ~ 90% sensitive and 90% specific. When positive in a patient with GPA, it is virtually always **c-ANCA** (96%).

The additional important positive antibody is anti-PR3.

Confirm diagnosis from either a biopsy of the nasal membrane or a lung biopsy. A kidney biopsy usually is not part of the diagnostic workup because it may not show the granulomas, is much more invasive, and doesn't allow for differentiation between forms of vasculitis.

Treatment for GPA is **aggressive** because, without treatment, most patients die within 2 years. To induce remission, use **cyclophosphamide + corticosteroids**—usually for a minimum of 4–6 months.

Methotrexate and azathioprine are typically used for maintenance therapy.

Again: kidney, lungs, and sinuses. Consider GPA in any patient who presents with a purulent nasal discharge, epistaxis, and/or signs of a glomerulonephritis with hematuria. The patient is not dyspneic and may or may not have a nonproductive cough or hemoptysis. If similar presentation but **ANCA-negative**, think **anti-glomerular basement membrane disease**.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis: 50% progress to **histiocytic lymphoma**. It is similar to GPA but has **no** upper respiratory lesions and only rarely affects the kidney. Although the principal site is the lungs, lymphomatoid granulomatosis less often has **skin**, **CNS**, and peripheral nerve involvement. Biopsy shows a mononuclear angio-centric necrotic vasculitis.

Quick Quiz

- What are the indications for treatment of sarcoid with corticosteroids?
- What is a potential lung complication of lymphangioleiomyomatosis?
- Characterize the typical presentation of a patient with granulomatosis with polyangiitis.
- Which vasculitis is c-ANCA+ and anti-PR3+?
- An asthma patient with worsening symptoms and peripheral eosinophilia makes you think of what diseases?
- Churg-Strauss vasculitis is associated with what medications?
- Which hepatitis virus is associated with PAN?
- How does PAN present?
- What do you do to diagnose PAN?
- Describe the differences in the presentations of Löeffler syndrome, acute eosinophilic pneumonia, and chronic eosinophilic pneumonias.

It is usually treated with corticosteroids and cyclophosphamide.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS; also called allergic granulomatosis and angiitis) is a **necrotizing, small-vessel vasculitis** with **eosinophil** infiltration. It can affect multiple systems and also cause neuropathy. It does not affect the sinuses.

Patients usually present with preexisting **asthma** and have eosinophilia up to 80% of the WBCs. Think about CSS (and ABPA) when assessing a progressively worsening asthmatic.

CSS may be unmasked by treating the asthmatic patient with a **leukotriene-receptor modifier** while weaning oral corticosteroids.

Treatment of CSS is mainly with systemic corticosteroids. Refractory cases are treated with cyclophosphamide, azathioprine, or high-dose IV immune globulin.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis causes an ILD in which there are masses of granulomata in the walls and surrounding tissues of airways.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is the only one of this group that is **not granulomatous**. It is a systemic, necrotizing

nongranulomatous vasculitis of small and medium-size arteries that can result in characteristic arterial aneurysmal dilatations.

The most common organs affected are intestinal mesentery, heart, skin, kidneys, testes, and peripheral nerves. PAN usually spares the lungs!

Many cases are associated with chronic hepatitis B infection.

Think about PAN in the patient with **+HBsAg** who presents with **constitutional symptoms** (anorexia, fever, malaise, weight loss) and any combination of:

- skin nodules,
- episodic abdominal pain, and
- tender testicles.

Lab studies show increased ESR and anemia of inflammation +/- p-ANCA and anti-myeloperoxidase.

Diagnosis rests on demonstration of non-granulomatous vasculitis in the tissues of the lung, kidneys, skin, or testes (ouch!). If biopsy is non-diagnostic or tissue is unapproachable, angiogram that demonstrates aneurysms in small and medium-size vessels is enough for diagnosis.

Remember that necrotizing granulomas are associated with GPA, and granulomas with eosinophils in the tissue are associated with Churg-Strauss.

Treatment for PAN is combination cyclophosphamide (Cytoxan®) and prednisone +/- treatment for HBV.

Eosinophilic ILDs

Overview

The eosinophilic ILDs are **eosinophilic pneumonia**, **ABPA**, and **Churg-Strauss syndrome** (discussed earlier on this page). Remember that asthma, hypereosinophilic syndrome, certain parasite infections, and some drugs are non-ILD causes of **peripheral** eosinophilia.

Eosinophilic Pneumonias

In all types of eosinophilic pneumonia, you must **rule out drugs and parasites** as the cause. Eosinophilic pneumonia consists of 3 types:

- 1) Löeffler syndrome. This disease is usually self-limited and occurs as a result of transpulmonary passage of helminthic larvae early in their life cycle. Usual cause is *Ascaris*, but other helminthes—*Strongyloides* or hookworms—are less common causes. Usually found incidentally. Minimal respiratory symptoms. These patients have migratory peripheral infiltrates on chest x-ray. Eosinophils are in the blood and sputum.

Treatment: no specific lung treatment unless severe, then corticosteroids. Do give antihelminthic therapy (albendazole, mebendazole, or pyrantel pamoate).

- 2) Acute eosinophilic pneumonia: an acute, febrile, pulmonary illness with hypoxemic respiratory failure resembling ARDS. Unknown cause. Rule

out infection. BAL shows large number of eosinophils. Treatment is ventilatory support and systemic glucocorticoids.

- 3) **Chronic** eosinophilic pneumonia: the **most common** eosinophilic pneumonia in the U.S.; it usually occurs in middle-aged women. The illness is subacute with cough, wheezing, night sweats, and low-grade fever. 50% have a history of asthma. The chest x-ray shows bilateral, very peripheral infiltrates in a pattern that is the photographic negative of pulmonary edema. (Instead of a butterfly pattern of whiteness, the chest x-ray butterfly pattern looks dark.) Increased number of eosinophils in the BAL, but 1/3 have no peripheral eosinophils. Very high ESR. Treatment is long-term steroids; relapses are common.

Allergic Bronchopulmonary Aspergillosis (ABPA)

Allergic bronchopulmonary aspergillosis (ABPA) is caused by an **allergic** reaction to *Aspergillus* that results in chronic cough, mucus plugging, and recurrent pulmonary infiltrates, with eosinophilia in some asthmatics and patients with CF.

Diagnosis: Think about ABPA in the patient with either **asthma or CF** who has uncontrolled disease; look for eosinophilia and *Aspergillus* growing in a sputum culture. In **asthmatics**, the clinical history may be recurrent exacerbations that improve with prednisone with return of wheezing, coughing, and dyspnea shortly after stopping steroids.

Chest x-ray and HRCT show central mucus impaction and bronchiectasis causing a “**fingers-in-glove**” appearing central infiltrate. Sputum may show branching hyphae (nonspecific). If there is only lung eosinophilia (no peripheral eosinophilia), consider a chronic eosinophilic pneumonia instead.

Screen for ABPA using the *Aspergillus* antigen skin prick test. If the skin test is positive, then work up the patient further by measuring a total IgE (usually > 1,000 IU/mL) and *Aspergillus* IgG and IgE. These antibody levels, plus the clinical history and other lab/x-ray data, can be reviewed in consideration of some major and minor criteria for ABPA (which you do not need to know for the Board exam). Just know when to suspect ABPA and that diagnosis starts with the pin prick test.

Treatment of active ABPA is itraconazole and oral steroids. In most patients, the addition of itraconazole will reduce the necessary duration of steroids, thus reducing long-term side effects.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) causes intermittent pulmonary **hemorrhage**. DLCO can be elevated. IPH is similar to Goodpasture's, **except** IPH does **not** affect the kidneys. Macrophages are filled with hemosiderin. Fe deficiency anemia occurs. It may remit in young patients, but it is unrelenting in adults. Remember that pulmonary hemorrhage also occurs in SLE.

DIAGNOSIS OF ILDs

PFTs in ILD patients classically show a “**restrictive**” pattern. This means normal airway flow rates, but lung volumes are decreased. There is increased lung stiffness from increased elastic recoil (increased by pulmonary fibrosis; decreased in emphysema). A chest x-ray with diffuse interstitial infiltrates is often the first suggestion of disease, but it correlates poorly with severity of disease. The HRCT is integral in the workup of ILD.

X-ray clues suggesting cause of ILD:

- Asbestosis: lower lung field predominance of infiltrates +/- pleural calcifications and plaques
- Silicosis: hilar eggshell calcifications
- Sarcoidosis: bilateral symmetrical hilar and paratracheal lymphadenopathy
- LAM: ILD with a pneumothorax in a premenopausal woman; may also have chylous effusions and characteristic nodules and cysts on CT

Bronchoscopy with transbronchial biopsy is the usual method for **confirming** the diagnosis and establishing the etiology and severity of ILD. However, the tissue specimens are small, and the best use of this technique is to diagnose and rule out the following:

- Diffuse infections
- Diffuse lymphangitic spread of carcinoma
- Sarcoidosis

Thoracoscopic biopsy (through the chest wall) and lung biopsy generally give the best yield for interstitial pneumonitis.

Remember that the DLCO is the **first** test to become abnormal in developing ILD, so it should be followed in patients receiving potentially lung-toxic drugs; e.g., amiodarone and chemotherapy.

NONINTERSTITIAL DIFFUSE LUNG DISEASES

Alveolar Proteinosis

Alveolar proteinosis is usually more alveolar than interstitial. There are defective alveolar macrophages causing a buildup of pulmonary surfactant.

Consider this in males, ages 30–50 years, who present with an indolent but progressive history of non-productive cough, dyspnea with exertion, weight loss, and occasional fever. Patients may be hypoxemic from a large R-to-L shunt with secondary polycythemia.

HRCT shows **ground-glass** appearance (similar to early IPF), along with thickened interlobular structures.

Diagnosis is usually confirmed with lung biopsy, but transbronchial biopsy or BAL is also okay.

Quick Quiz

- What is the workup of the uncontrolled asthmatic whom you suspect has ABPA?
- Which organisms are associated with chronic pneumonia in patients with pulmonary alveolar proteinosis?
- Name 4 autoimmune diseases associated with pulmonary hemorrhage.
- What common physical exam findings are seen in pulmonary hypertension (PH)?

Treatment: Smoking cessation is extremely important. If severe, do a whole lung lavage under general anesthesia. GM-CSF is a treatment that may restore proper function to the alveolar macrophages. Non-resolving pneumonias in these patients are most likely to be caused by *Nocardia*, mycobacteria, or endemic fungi.

Anti-GBM Disease

Anti-GBM disease can present as a pulmonary-renal disease, and a certain subset may present with diffuse pulmonary hemorrhage (Goodpasture syndrome). This is discussed in the Nephrology section, Book 2.

PULMONARY HEMORRHAGE

Immunologic lung diseases that cause pulmonary hemorrhage:

- Goodpasture syndrome
- SLE
- Granulomatosis with polyangiitis (previously “Wegener’s”)
- IPH

Cardiopulmonary diseases that cause pulmonary hemorrhage:

- Pulmonary AV malformations
- Aortic aneurysm
- Pulmonary hypertension
- Septic emboli
- Mitral stenosis

Other causes of diffuse alveolar hemorrhage and/or pulmonary hemorrhage include:

- Bronchitis
- Bronchiectasis
- Tuberculosis
- Lung abscess
- Aspergilloma

- Severe thrombocytopenia or coagulopathy
- Aspergillosis, zygomycosis (mucormycosis), and other acute fungal infections
- Chemotherapy and bone marrow transplantation

PULMONARY HYPERTENSION

OVERVIEW

Definition of pulmonary hypertension (PH): The **mean** pulmonary artery pressure is ≥ 25 mmHg at rest and ≥ 30 mmHg with exercise.

The World Health Organization (WHO) categorizes PH into **5** groups based on **etiology**:

- **Group 1 PAH** (pulmonary **arterial** hypertension) is composed of both idiopathic PAH (IPAH; previously primary pulmonary hypertension) **and** secondary PAH caused by diseases or toxins that damage small muscular pulmonary arterioles, such as collagen vascular diseases, intracardiac shunts, portal hypertension, HIV, and appetite suppressants/stimulants.
- **Group 2 PH** is due to **left-sided heart** disease (atria, ventricle, valve).
- **Group 3 PH** is associated with disorders of the **respiratory system** (ILD, COPD) or hypoxemia (e.g., sleep apnea).
- **Group 4 PH** is caused by **chronic venous thrombo-embolic** disease.
- **Group 5 PH** has unclear multifactorial causes, inflammation, mechanical obstruction, or extrinsic compression of the pulmonary vasculature.

Note that group 1 is pulmonary **arterial** hypertension (PAH). That is, PH caused by factors affecting the pulmonary arteries. Groups 2–5 are pulmonary hypertension (PH).

PH affects the entire vasculature of the lung, including the endothelium, smooth muscle, and even the extracellular matrix. This results in an **obliterative** process in which the pulmonary vessels become more tortuous and close off.

PHYSICAL FINDINGS OF PH

Physical exam: loud 2nd heart sound (P₂), tricuspid regurgitation, RV heave.

Tricuspid regurgitation is common with pulmonary hypertension and is due to the dilation of the right ventricle (holosystolic murmur along the LLSB—increases with inspiration—and a parasternal heave). The tricuspid regurgitation and right ventricular failure present as JVD with large **v** waves, liver pulsations, and lower extremity edema.

Chest x-ray is not used in the workup but might clue you in to an undiagnosed case—significant PH manifests on the chest x-ray as enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in “oligemic,” darker lung fields on chest x-ray.

DIAGNOSIS OF PH

ECG may show right axis deviation from RVH. The first tests to order when you suspect PH are **ECG** and an **echocardiogram**.

The echocardiogram is useful in the workup of PH to:

- Estimate pulmonary artery pressure
- Evaluate right ventricular size, wall thickness, and systolic motion
- Evaluate right atrial size
- Evaluate the presence of a R-to-L shunt through a patent foramen ovale (usually an agitated saline infusion is given—sometimes termed a “bubble echo”)

Right heart catheterization is then used to follow up PH diagnosed by echocardiogram. For a positive diagnosis, mean pulmonary artery pressure is, as stated earlier, ≥ 25 mmHg at rest and ≥ 30 mmHg with exercise.

Additional findings that support the diagnosis of **group 1 PAH** include:

- Pulmonary artery diastolic pressure (PADP) greater than PCWP
- Pulmonary artery mean pressure > 10 mmHg more than PCWP
- Pulmonary vascular resistance > 120 dynes-sec-cm⁻⁵

Remember that most pulmonary function parameters are normal in PH, but the DLCO decreases. Know that a low DLCO is associated with a poor prognosis in patients with PH.

TREATMENT

Exercise, Anticoagulants, Diuretics, and Oxygen

Exercise appears to improve the functional class of patients greatly but does not change the hemodynamics.

Give anticoagulants for those with IPAH (part of group 1) and for those with group 4 PH. Use warfarin to INR of 2.0.

Diuretics are recommended for fluid retention.

Oxygen helps symptoms in group 3 and also helps correct hypoxic vasoconstriction. Give oxygen to all who meet the criteria as discussed in COPD (page 3-17). Occasionally, **single-lung** transplantation or **heart-lung transplantation** are long-term solutions.

Vasodilators in PH

Most of the following have been tested only with IPAH (part of group 1 PAH).

Vasodilators — Endothelin Receptor Antagonists

Bosentan (Tracleer®) is an oral endothelin receptor antagonist. Endothelin is a polypeptide released by injured endothelium and is elevated in patients with PH and heart failure.

Ambrisentan and sitaxsentan are oral medications that are selective Type A endothelin receptor antagonists.

Vasodilators — Calcium Channel Blockers

The pulmonary vasodilators of choice are the calcium channel blockers—especially nifedipine, amlodipine, and diltiazem. Use amlodipine especially if intolerant of other calcium channel blockers, and diltiazem especially if tachycardic.

Short-acting pulmonary vasodilators, such as inhaled nitric oxide and IV adenosine, have only a transient effect. These are used in the workup of IPAH, testing for vasoreactivity.

Vasodilators — Prostanoids

Continuous IV (pump) infusion of **epoprostenol** (prosta-cyclin) has now been approved and is recommended as 1st line therapy for NYHA Class IV disease. It has shown good results for functional Class III also, but there are many other agents to choose from for Class III disease.

Know that patients getting epoprostenol exhibit tachypnea and require slow “ramp-up” of the dosing over time.

Iloprost, an inhaled vasodilator, helps with symptoms, but improvement in survival has not been demonstrated.

Vasodilators — PDE Inhibitors

Sildenafil (Viagra®, Revatio™) inhibits cyclic guanosine monophosphate (cGMP) phosphodiesterase type 5 (PDE-5) in smooth muscle of pulmonary vasculature, where PDE-5 is responsible for the degradation of cGMP. Increased cGMP concentration results in pulmonary vasculature relaxation, and vasodilation in the pulmonary bed may occur.

Vasodilators — Combination Therapy

Usually only 1 vasodilator is used. There is very little experience with combination therapy. Trials are ongoing.

VENOUS THROMBOEMBOLIC DISEASE

OVERVIEW

Venous thromboembolic disease (VTE) is the term that includes both deep venous thromboses (DVT) and pulmonary emboli (PE). DVT and PE are considered different parts of the **same** disease process; the majority of medically significant PEs are from DVT in lower extremities—virtually all from above the knee (ileofemoral area). Most calf vein thromboses do not embolize.

Other sources of PE are upper extremity, internal jugular, and subclavian thrombi. Usually the source for the **upper body** thrombi are **IV catheters**.

PE is the 3rd most common cardiovascular cause of death (after ischemic heart disease and stroke); 11% die

Quick Quiz

- What are the first tests you order in the workup of PH? What follow-up test is done if the first tests are suggestive?
- What test of lung function, when low, is associated with a poor prognosis in pulmonary hypertension?
- What is the usual cause of pulmonary emboli in hospitalized patients?
- What symptoms and physical exam findings are seen more with a submassive PE?
- Characterize the clinical findings seen with a massive PE.
- What is the first step in evaluating a patient with possible pulmonary embolism?

within 1 hour of onset of symptoms. Despite our knowledge of the cause and effect of PE, the **incidence** has **not** declined. In hospitalized patients, inadequate VTE prophylaxis is the usual cause of PEs.

The sequence of events in a medically significant PE:

- 1) Embolic obstruction of a pulmonary artery
- 2) Increased alveolar dead space—ventilated but not perfused
- 3) Vascular constriction
- 4) Loss of alveolar surfactant with atelectasis—V/Q mismatch + shunt areas

These events result in an increased resistance to blood flow → increased pulmonary artery pressure → increased right ventricular work. The pulmonary circulatory system is highly compliant and therefore inherently has high **capacitance**. Because of this capability, up to **50%** of the lung vasculature can be blocked before increased workload on the right ventricle becomes significant. Massive PE occurs when $> 2/3$ of a lung is involved.

Note that lung-tissue infarction is rare ($< 10\%$) because the tissue is fed by **multiple sources**, including the **bronchial artery**, the **PA**, and **back-diffusion** through the pulmonary venous system.

DIAGNOSIS OF PE

Overview

There are many diagnostic tests that are used in the workup of DVT and PE. We will go over clinical findings of PE first, then go over all the diagnostic tests, and then have a brief (whew!) discussion on working up PE that brings it all together.

Physical Findings in PE

Clinical findings are varied and usually nonspecific, but there is a suggestive **set** of signs and symptoms. Sudden onset of dyspnea and tachypnea are most common. Hemoptysis and pleurisy indicate associated lung **infarction**.

PE are divided into 3 groups: “**massive**,” “**submassive**,” and “**low-risk**.” The definitions are important for determining prognosis and for ascertaining which patients should be given thrombolytics:

- 1) The “massive” PE is defined as having sustained hypotension, pulselessness, or persistent, profound, bradycardia.
- 2) The “submassive” PE is defined as having normal blood pressure but evidence of RV dysfunction. It often has elevated troponins.
- 3) The “low-risk” PE is defined as resulting in normal blood pressure and normal biomarkers.

The **Wells prediction rules** determine the **pretest** probability of PE based on clinical findings and medical history. As we’ll discuss later, assessing these (or similar verified pretest probability rules) is the **first** step of the diagnostic workup for PE (**Table 3-9** and **Table 3-10**).

Malignancy is present in 50% of patients with **phlegmasia cerulea dolens** (an unusual type of DVT associated with additional thrombosis of collateral veins, which causes massive edema, pain, and blue discoloration due to arterial insufficiency). Malignancy also is suggested by superficial migratory thrombophlebitis, DVT resistant to anticoagulants, and thrombophlebitis in unusual places such as the arms and trunk.

Review of Lab and Radiological Tests for PE

Here we discuss 11 tests and how they are used to diagnose PE and determine the patient’s prognosis. In the next topic we put it all together and cover how PE is diagnosed.

These are the 11 tests. Know all of them:

- 1) ABGs
- 2) Chest x-ray
- 3) ECG
- 4) CTPA (using hCT)
- 5) V/Q scan
- 6) Venous studies
- 7) D-dimer
- 8) Pulmonary angiography
- 9) MRI/MRA
- 10) Echocardiography
- 11) Serum troponins

Draw an **arterial blood gas** (ABG) immediately. It is used to determine the A-a gradient and evaluate for

hypoxemia. Analysis of data from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) indicates that neither ABG nor A-a gradient is **specific** enough to be useful in the diagnosis or triaging of patients with pulmonary embolism.

Let's see why this is. An A-a gradient > 20 mmHg is seen in 89% of patients with a PE (pretty good sensitivity), but many people with cardiopulmonary disease have an increased gradient—and those hyperventilating or on O₂ may have an artificially low A-a gradient

(low specificity). So, **only** in the **absence** of cardiopulmonary disease **and** if the patient is not on O₂ **and** is not hyperventilating is there a satisfactory specificity for diagnosing a PE solely from an elevated gradient.

Hypoxemia, after a large PE, is due to many factors—especially V/Q mismatch, R-to-L shunt, and dead space—although dead space must be very large to cause hypoxia. The V/Q mismatch is from decreased perfusion of ventilated areas. The shunt is from perfusion of poorly **ventilated** areas that occur as a side effect of PE (2° to bronchoconstrictive mediators and atelectasis). Secondary right ventricular failure can also contribute to the V/Q mismatch.

Table 3-9: Wells Criteria for DVT

Criteria	Score
Active cancer (Current Tx or palliation, or Tx within last 6 mo)	1
Recent immobilization of lower extremities (plaster cast, paralysis, paresis)	1
Recently bedridden > 3 days or major surgery with general/regional anesthesia	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral nonvaricose superficial veins	1
Alternative diagnosis is at least as likely as DVT	-2
3 or higher = high probability of DVT 1-2 = moderate probability 0 = low probability	
Note: If symptoms are in both legs, use the more symptomatic one.	

Table 3-10: Wells Criteria for PE

Criteria	Points
Clinical signs of DVT	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate > 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (being treated, treated in the past 6 mo, or palliative)	1.0
0-1 = Low probability of PE 2-6 = Moderate probability > 6 = High probability	

Chest x-ray helps exclude other causes in the differential (**pneumonia**, **pneumothorax**). Chest x-rays are commonly either normal (12%) or nonspecific (infiltrate, effusion, atelectasis). Even so, a PE is suggested by:

- Pulmonary infiltrate with a normal WBC count on peripheral smear
- Pulmonary consolidation associated with an elevated ipsilateral hemidiaphragm (from atelectasis)
- “Hampton hump”—a pleural-based, wedge-shaped defect from infarction just above the diaphragm
- Oligemia (Westermark sign; rarely seen)—a lack of vascular markings in the area downstream of the embolus
- Large right descending pulmonary artery

ECG. The only specific (but not sensitive) heart/ECG changes seen with PE are tachycardia and right ventricle strain from acute cor pulmonale. On ECG, right heart strain = S1Q3T3; that is, the S wave is large in I, the Q wave is large in III, and the T wave is inverted in III. This is not seen often, but it is emphasized on Board exams. ECG also helps rule out MI.

CT pulmonary angiogram (CTPA; page 3-2). CTPA is the current standard for primary, noninvasive imaging, to diagnose PE—especially when the patient has cardiopulmonary problems that might obscure the results of the V/Q scan. Only in the setting of chronic venous thromboembolic disease as a cause for recurrent PE is the V/Q scan preferred over CTPA. CTPA also is the test of choice for diagnosis of PE in pregnancy.

Ventilation/Perfusion lung scan remains useful in obese patients, in those with iodine allergy, and in patients with renal insufficiency when contrast dye is undesirable. The V/Q scan is the test of choice for diagnosis of recurrent PE due to chronic venous thromboembolic disease.

Normal: A normal chest x-ray plus a normal V/Q scan is associated with a **very low risk of PE**. When coupled with a low clinical probability, a normal V/Q scan eliminates the diagnosis of PE.

Quick Quiz

- What happens to the A-a gradient in most patients with PE?
- What is the imaging of choice to diagnose pulmonary embolism in the non-pregnant patient with normal renal function and no dye allergy?
- In a low clinical probability scenario, what would a normal V/Q scan imply with regards to the probability of a pulmonary embolism?
- In a patient with a low clinical probability of venous thromboembolism, what is the significance of a negative D-dimer? A positive one?

Low-probability and **moderate-probability** scans are considered indeterminate because these patients have 14–40% chance of PE.

Moderate-probability scans consist of subsegmental perfusion defects or matched ventilation and perfusion defects. A chest x-ray finding of an infiltrate in the area of perfusion defect indicates the same risk. If clinical suspicion of PE is low, no further testing is necessary. If it is high, do a pulmonary arteriogram or U/S of the lower extremities.

High-probability scans occur in 2 situations:

- 1) ≥ 2 segmental or larger perfusion defects are present with a normal ventilation study.
- 2) The perfusion defect is much larger than the ventilation defect.

The trouble with V/Q scans is that large numbers come back as low-probability/indeterminate. You greatly improve accuracy of the above scans by factoring in clinical probability of a PE. For instance:

- About 30% of patients with a low-probability scan have a PE; but with a low clinical probability, this rate drops to 2%! And with a high clinical probability, it jumps to 40%.
- About 85% of patients with a high-probability scan have a PE; but with a high clinical probability, this rate jumps to 96%! And with a low clinical probability, it plummets to 6%.

Determining the probability for PE (by means of verified criteria such as Wells) is included as the 1st step of the diagnostic workup.

Venous studies. Determining the existence of DVT of the lower extremities is important in diagnosing and preventing PE.

Note that the current trend is to label venous thrombosis in the calf as simply “calf vein thrombosis” rather than DVT—because these clots do not carry the same morbidity as the more proximal thromboses (i.e., DVT).

Duplex ultrasonography combines real-time, B-mode ultrasonography, which visualizes the vessel with

Doppler flow detection, with looking for **compressibility** of vessel and **flow**. This test is reliable only in **symptomatic** patients being evaluated for their **first** DVT by an **experienced** operator (operator-dependent). In these patients, the sensitivity is 93% with a 98% specificity. It is poor for detecting distal DVT (because the vessels are hard to visualize) and abdominopelvic thrombi (from which most cases of PE arise).

hCT is better than ultrasound for detecting thrombosed vessels in the **abdomen and pelvis**. Some centers offer a “PE protocol” where they use some form of hCT technology to scan the lower extremity and lung vasculature to look for PE and DVT simultaneously.

D-dimer testing has become more sensitive and more useful. Used with any 1 of the above noninvasive tests, it increases the **negative** predictive value of the test.

A **negative** D-dimer in a **low-risk** patient **excludes** DVT/PE as a diagnosis.

Because of the **poor specificity**, the D-dimer has a poor positive predictive value, so do **not** use it to screen for DVT or PE.

Pulmonary angiography is the gold standard for diagnosis of PE. Because pulmonary angiography is an invasive test, it is reserved for cases with inconclusive results from CTPA and/or V/Q scan. It is used in patients who have a high clinical probability of disease but negative other studies, such as CTPA and Doppler U/S.

Pulmonary angiography, especially if selective (guided by V/Q or MDCT scan findings), is a relatively safe procedure. Mortality < 0.1%, morbidity = 1–2%.

MRI/MRA. MRI alone is showing good potential in visualization of the pulmonary vessels. MRA (angiography) is another, newer test with promise. It can view up to 8th order vessels. It is not available on all MRI machines. There is no set procedure for treatment of PE in subsegmental and smaller pulmonary emboli.

Echocardiography has poor sensitivity and specificity and is **not** indicated for the diagnosis of PE. However, it sometimes is used in the patient who has a presentation consistent with massive PE, so the diagnosis can be made at the bedside, and thrombolytics can be used.

Echo also is useful for making a prognosis in acute PE. Increased mortality is seen in patients who have normal blood pressure and evidence of RV dysfunction or presence of an RV thrombus.

Troponin I and T are elevated in 30–50% of submassive to massive PE's and are probably the result of right heart failure. They are mainly used to determine the prognosis. Elevated levels correlate with increased severity of PE and increased short-term mortality.

Putting It All Together: How to Diagnose PE

So, how is the diagnosis of PE made using these tests? It is really quite simple [**Know!**]:

- 1) Use clinical prediction rules (Wells = most commonly cited) to determine pretest probability of PE (Table 3-9 and Table 3-10).
- 2) In patients with low pretest probability, a negative highly sensitive D-dimer indicates a low likelihood of PE and excludes the diagnosis.
- 3) U/S of lower extremities is recommended for patients with intermediate-to-high pretest probability for PE. If high pretest probability and proximal (ileofemoral or higher) thrombi, treat for PE.
- 4) CTPA, V/Q scan, or standard pulmonary angiography is recommended in patients with intermediate or high pretest probability if lower extremity U/S does not show clot.

TREATMENT OF PE

Overview

Treatment for PE may include:

- Adjunctive treatment (O₂, hemodynamic support)
- Anticoagulants (heparins, fondaparinux, warfarin)
- Thrombolytics (streptokinase, tPA)
- Surgery (vena caval filters, thromboembolectomy)

Adjunctive Treatment for PE

Give oxygen for hypoxia. Many use **dobutamine** for right heart failure because it has both inotropic and pulmonary vasodilating effects.

Anticoagulants for PE

Overview

The main anticoagulants are **heparins**, **fondaparinux**, and **warfarin**.

Achieve adequate anticoagulation ASAP with a heparin or fondaparinux! It is indicated in **all** patients in whom PE is **suspected** or confirmed unless there are contraindications.

Anticoagulants are relatively contraindicated in the following:

- Uncorrected major bleeding disorder (thrombocytopenia, hemophiliias, liver failure, renal failure)
- Uncontrolled severe hypertension (systolic > 200 mmHg, diastolic > 140 mmHg)
- Potential bleeding lesions (active peptic ulcer, esophageal varices, aneurysm, recent trauma or surgery to head/orbit/spine, recent stroke, intracranial or intraspinal bleed)
- NSAIDs—increases GI bleed; if able, stop NSAIDs
- Repeated falls or unstable gait

Remember that pregnancy is an **absolute** contraindication for warfarin.

Contraindications require consideration of an IVC filter or thrombectomy/embolectomy.

Heparins

Overview: There are 2 types of heparin, unfractionated heparin (**UFH**) and the newer low-molecular-weight heparin (**LMWH**). LMWH is the drug of choice now for DVT and is at least as good as UFH for PE.

LMWH. Subcutaneous full-dose LMWH (tinzaparin, dalteparin, or enoxaparin) should be used whenever possible to treat PE (inpatients and outpatients) because of the lower risk of major bleeding compared to UFH. Either LMWH or UFH can be used for initial treatment of PE, although LMWH is preferred by most, especially if hemodynamically stable, because it reaches the therapeutic state faster.

LMWH is made from the depolymerization of heparin, which produces some molecular fragments with 30–50% the weight and more anticoagulant activity. LMWH has no effect on thrombin like UFH does—rather it solely inactivates factor Xa (so no effect on PTT). It has been proven to cause **fewer** instances of major bleed than UFH in DVT, and anticoagulation is established more quickly than with UFH in any VTE situation. LMWH still causes heparin-induced thrombocytopenia (although less often than UFH), so monitor platelet count.

LMWH is preferred for treating VTE in pregnant women, cancer patients, and anybody who will be treated for an extended period because the risk of osteoporosis is much less than with UFH. You can monitor activity by assessing activated Factor Xa levels, but this is not usually necessary.

LMWH should be used with caution in patients with estimated creatinine clearance of > 80 cc/min. It should not be used at all in patients with a clearance < 30 cc/min. Instead, use UFH because it can be titrated.

Patients who are at high risk for bleeds should be given UFH in an infusion, so it can be turned off and the effect reversed within a short period.

For both UFH and LMWH, protamine is the antidote for bleeding, but it is less effective against LMWH.

UFH binds with antithrombin (AT) to make it 1,000–4,000x more effective in inactivating thrombin and Factor Xa. To inactivate the thrombin, heparin binds to both the AT and the thrombin.

UFH is **no longer** the drug of choice for DVT, but it is still used for initial treatment of PE—especially if the patient is unstable. UFH dosage is determined by means of a **weight-based nomogram** to achieve adequate anticoagulation. Do PTT levels every 6–8 hours after dosage change to allow time to achieve steady state.

Quick Quiz

- Know perfectly the 4 items in the “Putting It All Together: How to Diagnose PE.”
- In what situations do you use low-molecular-weight heparin to treat thromboembolism? Unfractionated heparin?
- What effect does LMWH have on PTT? On factor Xa?
- Should PTT be monitored in patients on LMWH? How are factor Xa levels used?
- How does HIT present? Describe the treatment.

UFH is more often given to unstable PE patients because sub-Q LMWH requires good blood pressure and tissue perfusion for optimal delivery, and this situation is not present in unstable patients. (Thrombolytics are also used in unstable patients with PE. Know that you do **not** give tPA to **stable** patients with PE.)

Adjust the dose of IV UFH to keep the **PTT** at least 1.5x control for 7–10 days. Then continue anticoagulant treatment as discussed above (minimum **3–6 months**), preferably with either LMWH based on body weight or warfarin (see below). Adjusted-dose heparin is used by some—dosing to maintain PTT at 1.5x control. Greater increases than these result in increased **incidence of bleeding**.

Complications: The major problem with UFH use is hemorrhage. Before giving it, be sure the patient has no major bleeding syndrome, no recent bleed, and has heme-negative stool.

Heparin antidote: Again, for both UFH and LMWH, **protamine** is the antidote for bleeding. But it is less effective against LMWH.

Heparin-induced thrombocytopenia (HIT):

HIT Type **I** develops within 1–2 days of initiation of heparins. HIT-I is common and of **no** clinical consequence.

HIT Type **II** is an immune response where **antibodies** develop against the complex of heparin and platelet factor 4. The antibodies are named “anti-H-PF4.” HIT-II starts **4–10** days after initiation of treatment. It occurs in 1–3% of patients receiving UFH and about 0.5% of patients receiving LMWH. Arterial and venous thromboemboli are the major life-threatening complications. Always monitor the **platelet count** in patients on heparin; if it drops > 50% and/or thromboembolic symptoms develop, stop using heparin (even heparin flushes) and start treatment for HIT-II.

Treatment of HIT-II: **Stop** all heparin products and **start** anticoagulation with a direct thrombin inhibitor, such as lepirudin or argatroban. Start warfarin when the platelet

count recovers to $\geq 100,000$ (and continue the thrombin inhibitor) because there is a long-term risk of clots so long as the antibodies are present. Know that lepirudin should not be used in patients with chronic kidney disease. (“Be careful with le-**pee**-ru-din in those who can’t pee!”) Use argatroban instead.

Fondaparinux

This drug is a **Factor Xa inhibitor**. Give it sub-Q, once daily. It is approved for use in **DVT prophylaxis** of the surgical patient and for treatment of venous thromboembolism (both **DVT** and **PE**) as an alternative to UFH and LMWH. Fondaparinux does not cause HIT, so it is a useful drug for patients who need anticoagulation or prophylaxis and who have a history of HIT. Rate of bleeding is similar to heparins.

The drug is cleared exclusively by the **kidneys**, is contraindicated in patients with creatinine clearance < 30 cc/m, and probably should not be used when the clearance is between 30 and 80 cc/min because it accumulates. There is no way to monitor the effects of the drug, and there is **no antidote** for when patients bleed.

Warfarin

“International normalized ratio” (INR) is a product of the $PT_{\text{patient}}/PT_{\text{control}}$ ratio times an “international sensitivity index” (ISI). The ISI accounts for the sensitivity of the thromboplastin used by the lab, which varies from batch to batch. The formula is $INR = (PT_{\text{patient}}/PT_{\text{control}}) \times ISI$. INR is used to determine proper dosages of warfarin.

Warfarin is adjusted to increase INR to **2.0–3.0 (target 2.5)**. Initial dose is usually 5.0 mg/day, and this is often decreased to ~2.5 mg/day.

Note: Warfarin is a vitamin K antagonist that prevents activation of Factors II, VII, IX, and X.

Remember: After starting warfarin, Factor VII is the most rapidly decreasing **procoagulant**, but protein C (an anticoagulant) also decreases rapidly—so you may rarely see an initial net **procoagulant** effect. This may occur only until the slower-clearing Factor II decreases enough to result in a net anticoagulant state. This usually takes ~4 days. This potential problem is addressed by starting the warfarin right after heparin is started (within 8 hours), and keeping patients on heparin for at least 4 days.

Warfarin necrosis is an **idiosyncratic** side effect, which causes full-thickness skin necrosis requiring skin grafts.

Any decrease in the minimum level of dietary vitamin K will result in an increase in the INR. Monitor the INR more frequently if the **diet is changed** or the patient is **put on an antibiotic** that might kill the gut flora required for proper vitamin K absorption.

Warfarin interacts with many drugs. There is more on this in the General Internal Medicine section, Book 5, under Drug Interactions.

Do **not** give **warfarin** to **pregnant** patients (deformities are common, especially if given in the 1st trimester). Use LMWH or adjusted-dose UFH instead.

Note: In switching from heparin or fondaparinux to oral warfarin: Warfarin can be started at the same time or anytime after the heparin or fondaparinux is started. The **overlap** period should be at least **4–5** days (10 days with massive PE) with the INR at a therapeutic level for 2 days before discontinuing the heparin and continuing on the warfarin.

Remember that patients who are **pregnant** or who have **cancer** should be treated with **LMWH** for the entire treatment; warfarin is not indicated (and is contraindicated in pregnancy).

Thrombolytics for PE

PE: Streptokinase, tPA, and other thrombolytics are indicated for patients with massive PE who have “acceptable” risks of bleeding.

Submassive patients with prognostic risk factors for increased mortality may also benefit, if they are low-risk for bleeding.

Thrombolytics are not indicated for treatment of low-risk PE.

Vena Caval Filters for PE / VTE

Current indications for vena caval filters include recurring VTE with adequate anticoagulation or recurring VTE when anticoagulant treatment is contraindicated.

Retrievable vena caval filters may be used when only short-term protection is required, and can be removed when the risk for PE has subsided or when anticoagulation may be resumed.

Surgical thrombectomy/embolectomy is a potential option but is associated with high operative mortality.

Newer devices allow for mechanical thrombectomy (i.e., catheter extraction or AngioJet®) or mechanical disruption (i.e., pigtail catheters).

Putting It All Together: How to Treat PE

Know!

First, stabilize the patient: Put on O₂ and give hemodynamic support as needed with IV fluids and/or dobutamine.

Then, determine which anticoagulant to start. Usually it will be subcutaneous LMWH—especially if the patient is pregnant, has cancer, or is bedridden. If there is a history of HIT, fondaparinux is a good choice unless the patient has creatinine clearance < 80 cc/minute. In this case, argatroban, a direct thrombin inhibitor is your only choice. If the patient is unstable without a history of HIT, IV UFH is used (**PTT = 1.5x** control). If massive PE, consider thrombolytics.

In hospital, anticoagulant treatment is continued for **7–10** days. Home treatment with LMWH or warfarin is continued for **3–6** months for PE due to transient risk factors, **12** months for idiopathic PE, and **indefinitely** for recurrent PE or thrombotic tendencies.

And remember, if switching to warfarin: Before stopping heparin or fondaparinux, patient must have been on warfarin for **4–5** days and have had a therapeutic INR (2.0–3.0) for **2** days.

TREATMENT OF DVT WITHOUT PE

Know that if the patient has a high probability of DVT with a low probability of PE (or if these diagnoses have been confirmed), the treatment is **exactly the same as that for PE** (just above).

Although few **calf vein thromboses** migrate above the knee, the ones that do are usually **painful**! So historically, we have treated patients with a painful calf venous thrombosis with anticoagulants and observed the painless thromboses with serial ultrasound.

However, now there are **conflicting recommendations** among various IM societies about the treatment of painless and painful calf thromboses, with some societies advocating treating all cases with anticoagulation and other societies advocating treating only the painful ones—so, not a Board question!

RISK AND PROPHYLAXIS OF VTE

Overview

Pulmonary embolism is the most common preventable cause of death in hospitalized patients. Prophylaxis for DVT (and therefore PE) is cost-effective. In spite of the existence of numerous evidence-based guidelines, adequate prophylaxis is still not being offered to many medical patients (which makes this topic ripe for Board questions).

VTE Prophylaxis

ACP issued guidelines in 2011 for VTE prophylaxis, and the recommendations have simplified things some.

Know that **stockings are no longer recommended** for any patients because stockings can cause skin damage.

It is recommended that a risk assessment tool be used, but one was not suggested by ACP. Any assessment tool that considers a patient’s medical history and current conditions, then assesses for risk of bleeding, is adequate.

Unless patients are “very high risk” for bleeding, a drug for VTE prophylaxis is recommended. Types include subcutaneous LMWH and UFH. These drugs reduce the risk of PE, but not DVT or mortality.

Quick Quiz

- In what patients is warfarin absolutely contraindicated?
- When are thrombolytics used to treat pulmonary embolism?
- What are the indications for a vena caval filter?
- Know perfectly the 4 paragraphs in "Putting It All Together: How to Treat PE".
- What is the first choice for DVT prophylaxis in the hospitalized medical patient?
- Name the causes of transudative pleural effusions.
- What 3 conditions must be met to call an effusion a transudate?

For patients at the "highest risk" for bleeding, use pneumatic compression instead of drugs for VTE prophylaxis.

The use of fondaparinux is unclear because the heparins are considerably less costly. Probably "fonda" should be used as prophylaxis only in patients who have had HIT (if kidney function is okay).

FAT EMBOLI

Fat emboli cause the **triad** of dyspnea, confusion, and petechiae—usually in the neck, axilla, and/or conjunctiva. Fat emboli can occur within 72 hours after a **fracture** of a **large bone** (e.g., femur), sometimes **after CPR**, and with **sickle cell** bone-occlusive crisis.

Treatment is supportive; unless the patient has secondary ARDS, corticosteroids have **not** proven helpful.

PLEURAL EFFUSIONS

EXUDATIVE vs. TRANSUDATIVE

Overview

Pleural effusions are either transudative or exudative (Image 3-12).

A **transudative** effusion is a secondary phenomenon, due to **systemic** changes influencing the formation and absorption of pleural fluid. The most common causes are LV failure, cirrhosis, and nephrotic syndrome.

An **exudative** effusion is due to a **local** cause, and the 2 most common ones are bacterial pneumonia and cancer—but don't forget pulmonary embolism, even though it is not as common.

Table 3-11 details the results of fluid studies that help you determine whether a pleural effusion is a transudate

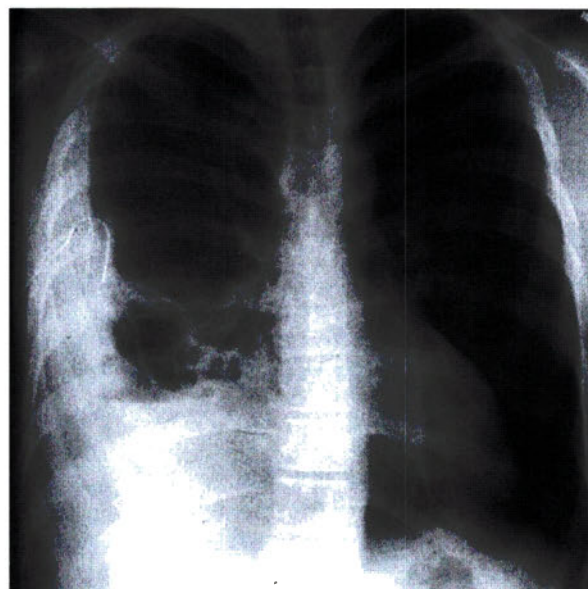


Image 3-12: PA Chest: Right-side pleural effusion

or an exudate. These measurements and ratios that determine the diagnosis of "exudates" are called the Light Criteria. Note that **all 3** conditions must be met for an effusion to be called a transudate—failing any 1 criterion makes it an exudate.

Transudative effusions require no further workup because they are reactive, systemic phenomena—treat the main problem.

Exudative effusions are associated with local disorders and require further tests on the fluid to establish the cause. For this reason, you will want to send several tubes of pleural fluid to the lab. Evaluate the first tube; then tell the lab to save the rest. Once you know the type of effusion, then you can decide on the other tests.

Transudative Effusions

These effusions do not need further evaluation once you've definitely established that the fluid is a transudate.

Know that **LV failure** is the #1 cause, and it is not unusual to see an isolated right-sided effusion. You may see left-sided pleural effusion in association with pancreatitis. Transudative effusions are common after abdominal surgery and are usually benign.

Some experts advocate that bilateral effusions, equal in size and responsive to diuretics, in patients with well-established LV failure, cirrhosis, or nephrotic syndrome, do **not** need thoracentesis because the overwhelming majority will be transudates. But always tap unilateral, asymmetric, or nonresponsive effusions to characterize the fluid.

Table 3-11: Light Criteria for Pleural Effusions

	E/S Protein		LDH _{EFF}		E/S LDH
Transudative	< 0.5	and	< 200	and	< 0.6
Exudative	> 0.5	or	> 200	or	> 0.6

Relief of dyspnea after therapeutic thoracentesis for an effusion is due to a **decrease** in intrathoracic volume! This is because most of the volume a pleural effusion occupies is obtained by distending the diaphragm (which causes the dyspnea). Only about 20% of the volume is obtained from compression of the lung.

Exudative Effusions

From the get-go, once you get your LDH and protein results back on the fluid and serum, and you determine that your fluid is an exudate, tell the lab to do the following simple studies on the remaining fluid you sent:

- Glucose and amylase
- Cell count with differential
- Gram stain and bacterial culture
- Cytology
- Marker for tuberculosis (e.g., adenosine deaminase level), if available
- If the above studies do not help you with diagnosis, consider CTPA to evaluate for pulmonary embolism.

These initial studies, plus your clinical history and exam, will help you determine the most likely cause, which we will discuss next.

Bacterial pneumonia is the #1 cause of an exudative effusion in the U.S. The effusion develops in association with **bacterial** pneumonia or lung abscess (rarely, also with bronchiectasis). Consider the possibility of effusion every time you consider bacterial pneumonia as a diagnosis. If clinical evidence of effusion is present in the setting of pneumonia, quantify the size using imaging (chest x-ray, CT, or U/S). Key is **10 mm**! If there is more than 10 mm of fluid from lung surface to chest wall, the patient needs a thoracentesis—to get out the bulk of inflammatory material and organisms and to give the patient the best chance to heal.

The effusion is “**complicated**” if any of the following are found on analysis of fluid from the therapeutic thoracentesis:

- Loculations on imaging
- pH < 7.20
- Glucose < 60 mg/dL
- Positive Gram stain or culture

Empyema thoracis is the diagnosis when visible frank pus is found.

Treatment of a complicated effusion requires at the least a chest tube and may require surgical intervention.

Empyema thoracis often requires surgical therapy, and video-assisted thoracoscopic surgery (VATS) has recently become the best technique. VATS is supplanting thoracoplasty and decortication.

Malignancy is the 2nd most common cause of an exudative effusion. The most common malignant pleural

effusions are **lung** cancer (1/3), **breast** cancer (1/4), and **lymphoma** (1/5). Lung, breast, lymphoma ... 1/3, 1/4, 1/5.

In a pleural-based malignancy, cytologic examination of the effusion fluid has as high a yield as pleural biopsy! 3 effusion samples have a combined yield of > 90%. Thoracoscopy is done if the initial cytology is negative, and pleural biopsies are rarely needed anymore to diagnose cancer. The main use now for a pleural biopsy is to diagnose pleural TB.

Less common (but important!) causes of exudative pleural effusions: mesothelioma, pulmonary embolism, viral infections, and tuberculosis.

Mesothelioma. Think about mesothelioma (considered pathognomonic for asbestos exposure) in patients with dyspnea, chest pain, and a grossly **hemorrhagic** pleural effusion.

Pulmonary embolism. Consider this in the dyspneic patient with an exudative effusion showing normal fluid amylase, glucose > 60 mg/dL, normal or slightly increased cell count and differential, and Gram stain showing no organisms. PE as a cause of pleural effusion is often missed clinically!

Virus. Many viruses cause **self-resolving** pleural effusions. Think of a probable viral cause in someone who improves quickly without intervention.

Tuberculosis. Think of tuberculous effusion in the patient with risk factors for **primary** TB and additional history of fevers and wasting. Pleural fluid cell count usually is **lymphocytic**.

Mycobacterial-specific tests are now commercially available to diagnose TB in the fluid, and they are quite good. These are adenosine deaminase (ADA), interferon-γ release assay (IGRA) and polymerase chain reaction (PCR) for TB DNA.

If you do not have these special tests available, do a **pleural biopsy**. Send your tissue for routine pathology with AFB stains, and send a sample to the micro lab for AFB smears and culture. Aside from the special mycobacterial-specific research tests described above, path + cultures of pleura is the approach with the highest diagnostic yield for TB, between 65 and 90% (higher than any single approach). In clinical practice, closed pleural biopsies are rarely performed these days. Most of the pleural sampling procedures are now done with video-assisted thoracoscopic surgery (VATS), which has a high yield for diagnosis and is one procedure for both pleural fluid sampling and pleural biopsy.

Again: To diagnose cancer = repeat taps and cytology; to diagnose TB on a pleural effusion = pleural biopsy.

And one weird one: Think about “**yellow nail syndrome**” if the patient has a history of chronic peripheral edema

Quick Quiz

- What clinical and laboratory features make a pleural effusion “complicated”?
- What is the definition of “empyema”?
- What specific tests for *M. tuberculosis* are available to diagnose TB using pleural fluid?
- What is the procedure of choice on the Board exam for diagnosing pleural TB, if TB-specific fluid tests are not given as an option?
- What is the definition of hemothorax?
- Define “chylous” effusion. What causes it?
- What conditions are associated with secondary pneumothorax?

and chronic exudative pleural effusions. Patients with this genetically transmitted syndrome will also have yellow, dystrophic nails.

Some Key Effusion Findings

Cell count with differential findings. General clues:

- WBCs > 1,000, think exudate; > 10,000, think complicated parapneumonic effusion; WBCs > 100,000 = empyema or pus.
- Mesothelial cells normally line the cavity and are occasionally confused with malignant cells. There is a consistent finding that, with a tuberculous pleural effusion, there are very few mesothelial cells. So, if a high **mesothelial** cell count is reported in the fluid, then TB is highly **unlikely** to be the cause.
- Eosinophils > 10%: Think pneumothorax, drug reaction, post-thoracotomy, paragonimiasis (trematode: fluke), fungal infection, and asbestos exposure.
- Lymphocytes > 50%: Think TB or malignancy.
- Neutrophil predominance: Think pneumonia, pancreatitis, PE, peritonitis.
- Know the specific definition of **hemothorax**: grossly bloody pleural effusion with a hematocrit > 1/2 of the hematocrit of the peripheral blood. Think trauma!

Fluid chemistry findings:

- Glucose ~ 80 = TB; ~ 60 = cancer, empyema; < 30 = rheumatoid arthritis.
- Amylase increased in pancreatic fistula and esophageal rupture (salivary amylase).
- Adenosine deaminase (ADA) concentrations (especially isoenzyme ADA-2) are elevated in tuberculous pleural effusions. (Conversely, ADA level < 40 U/L is rarely TB.) This test is used as a diagnostic aid when a TB effusion is suspected but other tests are negative. Other tests include the γ -interferon and polymerase chain reaction to identify TB DNA.

What if the pleural fluid is milky white, but not pus?

Chylous effusions are white-colored, exudative effusions with a triglyceride level > 110 mg/dL (due to fat globules; i.e., chylomicrons). The chylous effusions are associated with leakage of thoracic duct lymph. Think **trauma** and **cancer**. Work hard to find the cause using imaging studies of the mediastinum.

Pseudochylous pleural effusions are associated with chronic inflammatory processes, especially TB and rheumatoid arthritis lung disease. Triglycerides in pseudochylous effusions are < 50 mg/dL; total cholesterol is > 65 mg/dL because the white color is due to cholesterol, not chylomicrons. Neither the chylous nor pseudochylous specimens clear with centrifugation.

PNEUMOTHORAX

Primary spontaneous pneumothorax (**PSP**) was once thought to be a benign problem that most commonly affects tall, slender, smoking men ages 20–40 years. With high-resolution CT, we now know that many of these patients have emphysematous blebs, which may be an etiologic factor.

Secondary spontaneous pneumothorax (SSP):

- COPD is the most common cause.
- *Pneumocystis* pneumonia in AIDS patients occasionally causes a pneumothorax.
- Cystic fibrosis.
- Eosinophilic granuloma (histiocytosis X—smoking males).
- LAM—exclusively premenopausal women.
- Mechanical ventilators—about 10–15% of patients develop barotrauma, including pneumothorax.
- Recurrence rate for PSP is 28%, while that for SSP is 43%. Risk of mortality is 1–4% for PSP and up to 17% for SSP.

Initial treatment: If the pneumothorax is small (< 15–20%) and the patient is stable, observe the patient and give high-flow O₂. 3 L/min O₂ by nasal cannula is associated with a 3–4-fold increase in rate of reabsorption (vs. room air).

If the pneumothorax is larger, place a small anterior chest tube. This may consist of an intravenous catheter inserted via the 2nd intercostal space, aspirated, and either closed off or connected to suction. A chest tube is mandatory in pneumothorax patients receiving positive pressure ventilation!

Review of pleurevac components (Figure 3-6).

3 chambers:

1st chamber (nearest the patient) = **Collection chamber**—where whatever effluent from the pleural cavity is collected.

2nd chamber (middle) = **Water-seal chamber**—allows air to bubble out from the pleural cavity but does not

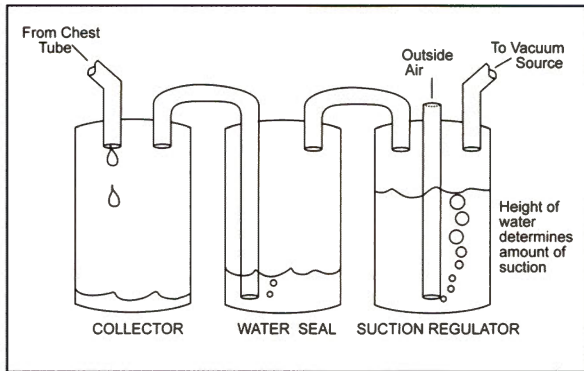


Figure 3-6: Pleurevac System

allow air into the chest. Bubbles in this chamber indicate air is in (or still entering) the pleural space.

3rd chamber (attached to suction) = **Suction regulator**—height of water determines the amount of suction on the chest tube (when vacuum is applied to the chamber and there is bubbling in the water of the chamber).

If there is a persistent air leak with < 90% expansion of the lung, video-assisted thoracoscopic surgery (VATS) is used to either staple the blebs or instill talc.

A persistent air leak for > 7 days suggests a bronchopleural fistula, which may require surgical intervention for stapling and pleurodesis to prevent recurrences.

Recurrence prevention: Pleurodesis decreases the recurrence rate significantly. Pleurodesis is **not** usually done with the 1st episode of **SSP** (usually done after 2nd), but it is reasonable to use it for the 1st. There is more evidence suggesting that you should do pleurodesis for even the 1st occurrence of PSP, and this may become the standard of care. Talc is the best and cheapest agent for pleurodesis. Doxycycline and minocycline are next. Bleomycin is too toxic and no longer recommended.

SINUSITIS / TONSILLITIS

Acute sinusitis is either viral or bacterial. Viruses (rhinovirus, influenza, parainfluenza) are the most common causes of acute sinusitis that lasts < 10 days. Bacterial sinusitis can complicate viral URIs. The most common bacteria are pneumococcus, *H. influenzae*, and *Moraxella*. Treat with TMP/SMX, AM-CL, clarithromycin, a 2nd/3rd generation cephalosporin, or fluoroquinolone. Treat recurrent sinusitis for 3 weeks. Osteomyelitis of the frontal bone is rare; it is indicated by a pale, cool edematous area over the forehead called **Pott puffy tumor**.

Postanginal sepsis (Lemierre syndrome) is an anaerobic sepsis secondary to thrombophlebitis of the jugular vein. This phlebitis is the result of spread from an adjacent tonsillar abscess.

PNEUMONIAS

OVERVIEW

Pneumonia is categorized in 1 of 4 ways:

- 1) Community-acquired (CAP)
- 2) Health care-associated (HCAP)
- 3) Hospital-acquired (HAP)
- 4) Ventilator-associated (VAP)

Currently, HCAP is defined to exclude HAP and VAP, but the next guidelines are likely to recategorize HAP and VAP as subsets of HCAP (logically!).

COMMUNITY-ACQUIRED PNEUMONIA

Overview

CAP can be organized into 2 groups based on the organisms that cause disease:

- 1) “**Typical**” (pneumococcus, *H. influenzae*, *S. aureus*, gram-negative rods, and *Moraxella catarrhalis*)
- 2) “**Atypical**” (*Mycoplasma*, *Chlamydia*, *Legionella*, endemic fungi [cocci, histo, blasto], and viruses [flu, adeno, RSV]). Atypical pathogens cannot be identified by Gram stain or routine bacterial culture (require special media), and they are resistant to β -lactam antibiotics, which are 1st line drugs for empiric treatment of CAP.

We usually never figure out which bug is causing a patient’s pneumonia, but there are some risk factors associated with certain pathogens. And these associations are often tested. They are discussed in the section on empiric treatment of CAP (page 3-46).

In 2007, the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) came together to give us guidelines for evaluating, diagnosing, and treating CAP. Think about CAP from 2 perspectives:

- 1) **Empiric** treatment; when the organism is not known
- 2) **Pathogen-directed** treatment; when it is known

Clinical Presentation of CAP

Symptoms are variable (from mild to severe) and include fever, anorexia, sweats, dyspnea, sputum production, cough, and pleurisy. Nausea, vomiting, and diarrhea occur in 20%. **Elderly** patients are also often **confused**.

Exam findings include tachycardia, tachypnea, evidence of consolidation (increased tactile fremitus, bronchial breath sounds, crackles), and/or parapneumonic effusion (decreased tactile fremitus and percussion).

There is **overlap** in signs and symptoms caused by typical and atypical pathogens—so you cannot use the history of symptoms or the x-ray findings to differentiate the 2.

Quick Quiz

- Which organisms are the common causes of bacterial sinusitis?
- What is Lemierre syndrome?
- Identify the organisms associated with “typical” and “atypical” CAP.
- When is it appropriate to start doing a full workup in CAP?
- Detail the characteristics that a sputum sample must have to be considered an adequate specimen.
- List the tests that you need to order in patients with severe or unresponsive CAP.

Diagnosis of CAP

Overview

These are the recommendations for diagnosis based on ATS/IDSA 2007 guidelines.

Bottom line: The initial workup of CAP is very **limited** if the patient does not have severe disease (i.e., requiring ICU) and responds to empiric therapy.

More **aggressive** workup is recommended for patients:

- with risk factors for severe disease (e.g., underlying structural lung disease or uncontrolled comorbidities),
- with a severe presentation (requiring ICU), and
- who are unresponsive to empiric treatment.

Diagnostic Tests

Chest x-ray is required for diagnosis in patients with CAP. Some confusion in reading the x-ray may result from HF, COPD, and malignancy. Remember that an infiltrate may not appear in a volume-depleted patient until after the patient is volume-resuscitated. See [Image 3-13](#) and [Image 3-14](#) for a comparison of middle lobe and lower lobe pneumonias.

Do a **sputum Gram stain and culture** in patients with:

- severe or unresponsive CAP,
- COPD,
- a history of alcohol abuse,
- cavitary infiltrates, and/or
- a pleural effusion.

In the intubated patient, send a deep-suction aspirate or sample from **BAL** (better than sputum) as soon as possible because targeted antibiotics in the ICU **do** affect outcome (as opposed to outpatients who do fine with empiric therapy).

Add an acid-fast stain if tuberculosis is in your differential based on the presentation and x-ray.

Do **not** do sputum tests on admitted patients who don't meet these indications or on outpatients with CAP.

Sputum interpretation: The C+S results are accurate only if there are > 25 neutrophils and < 10 epi's per low-power field. If more epithelial cells are present, then it is contaminated. If the patient gives you a cup with what looks like saliva mixed with a few mucoid globs, fish out these “goobers” and send them to the lab (higher yield)!

Blood cultures should be done on patients with:

- severe or unresponsive CAP,
- COPD,
- liver disease,
- a history of alcohol abuse,
- cavitary infiltrates,
- asplenia,
- a pleural effusion,
- leukopenia, and/or
- a positive pneumococcal urine antigen test.

Do **not** do blood cultures in admitted patients who don't meet these indications or on outpatients with CAP.

Other tests: In patients with severe CAP, add to blood and sputum cultures: urine antigen tests for pneumococcus and *Legionella*.

Additional admission tests are: CBC, Chem-6, liver function tests, O₂ sat, and HIV testing.

Serologic tests are usually **not** helpful in the initial evaluation. **DNA probes** and nucleic acid amplification are **not** indicated.

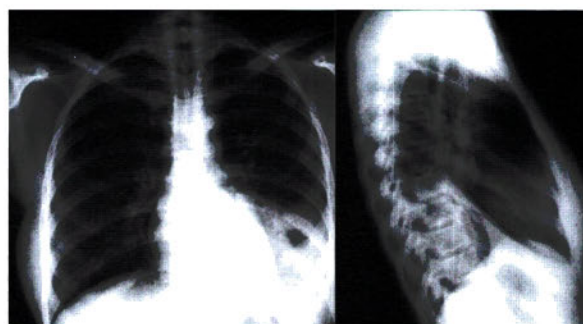


Image 3-13: Left lower lobe pneumonia

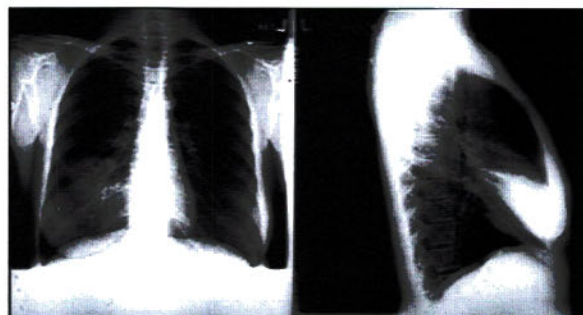


Image 3-14: Right middle lobe pneumonia

Treatment of CAP

Remember to think of CAP from 2 perspectives: **empiric** treatment and **organism-specific** treatment. The following treatment discussion is also based on the 2007 ATS/IDSA guidelines. Refer to [Figure 3-7](#) during the following discussion.

Empiric Treatment of CAP

Empiric treatment is started before pathogen identification and is based on:

- **Severity** of the illness and need for hospitalization: Assess every patient for admission using a severity scale, such as the pneumonia severity index (PSI) or the CURB-65. (Guidelines heavily emphasize use of these criteria!)

- **Likelihood** of a certain pathogen based on associated risk factors.

What you prescribe empirically is partly determined by whether the patient will be admitted (usually, outpatients = oral; inpatients = parenteral).

PSI vs. CURB-65

The PORT (Patient Outcome Research Team) Pneumonia Severity Index (PSI) ranges from **I** to **V**. It is a determination of outcomes based on initial presentation, and it is routinely used to determine the severity of pneumonia and whether the patient needs to be admitted to the hospital ([Table 3-12](#)).

This determination of severity is a 2-step process. The 1st step is to see if the patient is in risk **category I**; this is

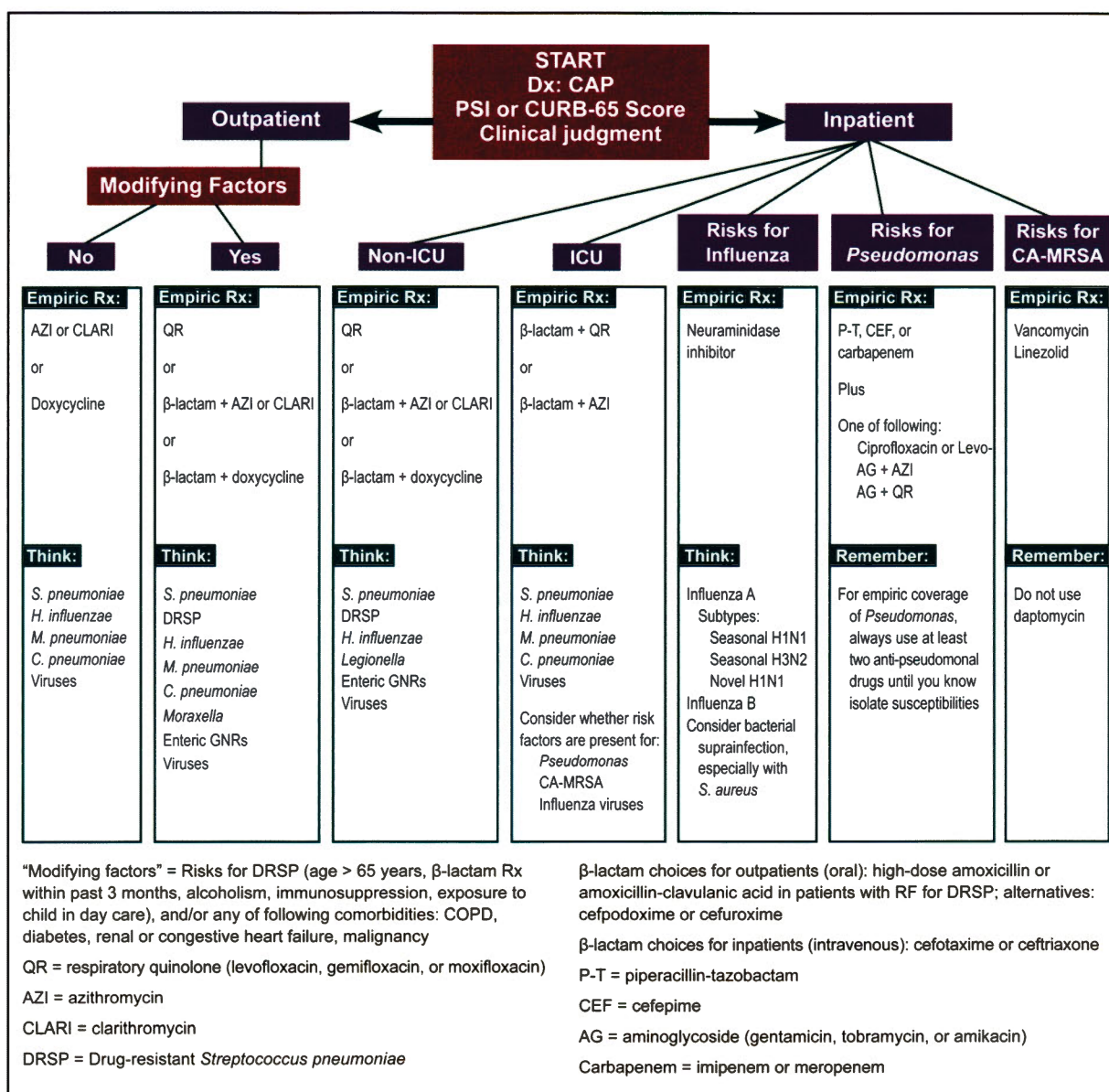


Figure 3-7: Treatment of Outpatient and Inpatient Community-Acquired Pneumonias

Quick Quiz

- Be familiar with the CURB-65 and the Pneumonia Severity Index (Table 3-12).
- Which patients are at increased risk for infection with DRSP?
- A patient with known influenza develops a cavitating pneumonia. Besides pneumococcus, what organism should you consider?

determined solely from the history and physical exam. Basically, if the patient is < 50 years of age, there is no history of comorbidity, and the physical exam is okay (normal mental status, pulse < 125, RR < 30, systolic BP > 90, and temp > 35° but < 40° C), then the patient is risk category I and **no** further workup is required.

If the patient is not assigned to risk category I, the next step utilizes results from blood tests (chemistry and ABG) and an x-ray (# of affected lobes, existence of pleural effusion). Based on these results, the patient is put in risk category II–V. Note the jump in mortality rate for risk category IV and V compared to I–III! For this reason, those with a risk category of **IV** or **V** are **admitted**. Those with I–III can be treated as outpatients.

CURB-65 is not as well studied as the PSI but is **easier and quicker**. The CURB-65 uses 5 variables:

- 1) Confusion
- 2) BUN > 20 mg/dL
- 3) RR ≥ 30 breaths/min
- 4) BP—systolic < 90 or diastolic ≤ 60
- 5) Age ≥ 65 years

Risk and mortality based on number of variables present:

- 0–1 = low risk
- 2 = moderate risk
- 3–5 = high risk

General interpretation of the CURB-65 is that the low-risk group will likely do fine as outpatients, while the patient with 2 or more variables should be admitted. The high-risk group should be considered for ICU admission.

A simplified CURB-65 drops the BUN, so assessment can be made in the office without lab work. Without the BUN, admit if patient has **1 or more** variables.

Pathogen Associations

Remember that you are **guessing** the most likely causal organisms when you are treating empirically. Know the following associations:

Pneumococcus is more likely in these groups: chronic diseases (heart, stroke, seizures, dementia, COPD, HIV/AIDS), cigarette smoking, and alcoholism. Resistance to β-lactams is **increasing** in pneumococcus. If your patient

has a resistant pneumococcus, he may not respond to empiric cephalosporin treatment (or not respond as well). Consider drug-resistant *S. pneumoniae* (**DRSP**) in these groups: age > 65 years, recent (3 mo) β-lactam therapy, alcoholism, immunosuppression, multiple comorbidities, and/or exposure to child in day care. (When discussing DRSP, generally the concern is resistance against penicillins, cephalosporins, macrolides, tetracyclines, and TMP/SMX. But know that pneumococcus is developing resistance against the respiratory quinolones as well.)

S. aureus pneumonia is associated with influenza virus as a bacterial **suprainfection**. Know that community-acquired MRSA (CA-MRSA) is now a cause of CAP and can be severe with necrotic complications. This CA-MRSA has special genetic endowments (superantigen genes, such as the Panton-Valentine leukocidin; PVL) that make it a particularly aggressive bug in patients without any underlying disease. CA-MRSA is more common in these groups: Native Americans, homeless, gay men, prisoners, military, day care, and contact sport athletes.

Table 3-12: The Pneumonia Severity Index (PSI)

Demographic Factors	Findings	Points Assigned
	Males Females Nursing home residents	Age (years) Age – 10 Age + 10
Comorbid Illnesses	Neoplastic disease	+ 30
	Liver disease	+ 20
	Congestive heart failure	+ 10
	Cerebrovascular disease	+ 10
	Renal disease	+ 10
Physical Exam	Altered mental status	+ 20
	Resp rate ≥ 30 bpm	+ 20
	Systolic BP < 90 mmHg	+ 20
	Temp < 35° C or ≥ 40° C	+ 15
	Pulse ≥ 125 bpm	+ 10
Laboratory	pH < 7.35	+ 30
	BUN > 10.7 mmol/L	+ 20
	Na < 130	+ 20
	Glucose > 139	+ 10
	Hct < 30%	+ 10
	P _a O ₂ (art) < 60 mmHg or O ₂ sat < 90%	+ 10
	Pleural effusion	+ 10
Scoring	Points	Mortality (%)
I	< 51	< 0.5
II	51–70	≥ 0.5–0.9
III	71–90	≥ 1.0–3.9
IV	91–130	≥ 4.0–9.9
V	> 130	≥ 10.0

Gram-negative organisms are associated with uncontrolled chronic diseases, immunosuppression, and alcoholism.

Legionella is associated with diabetes, cancer, kidney disease, HIV/AIDS, and a recent cruise ship or hotel stay.

Note that some of these risk factors might cause the pneumonia to be reclassified as HCAP (health care-associated pneumonia), depending on circumstances.

Know these organism-specific associations:

- COPD or immunoglobulin deficiency (especially IgG): *Moraxella catarrhalis* and *H. influenzae*
- Cattle or sheep exposure: *Coxiella burnetii* (Q fever)
- Bird fanciers: *Chlamydophila psittaci* (psittacosis)
- Hunters: *Francisella tularensis* (tularemia)
- Bat caves especially in the Mississippi and Ohio River valleys: *Histoplasma capsulatum* (histoplasmosis)
- Travel to California or Arizona: *Coccidioides immitis* (coccidioidomycosis)
- Living in or travel to central, southeast, and mid-Atlantic states, especially Illinois and Arkansas: *Blastomyces dermatitidis* (blastomycosis)
- Risk factors for HIV/AIDS or other immunocompromise: *Pneumocystis jiroveci* (PJP) and TB

Empiric Antibiotics

Refer to Figure 3-7 on the treatment of CAP as we go through this discussion. Know that identifying the specific microbial cause of CAP is expensive and difficult.

And, except in ICU cases, no data have shown that targeted treatment of a specific organism is superior to empiric treatment of possible organisms. Therefore, empiric treatment is accepted as appropriate and is emphasized by the guidelines as initially preferred over attempting to diagnose the microbial cause of CAP.

Outpatients

The majority of patients with CAP are treated as outpatients based on a severity index indicating low risk—with either macrolides (**azithromycin** or **clarithromycin**) or **doxycycline**. Note that **erythromycin** is a choice, but GI side effects limit its use, and it is less effective against *H. influenzae* than the advanced macrolides.

If the patient has risk factors for DRSP or has comorbidities that could affect outcome (termed “modifying factors”), use a respiratory quinolone or high-dose amoxicillin (because the resistance can sometimes be overcome with larger β -lactam doses). An alternative is to pick an oral cephalosporin with known activity against DRSP.

Inpatients — Non-ICU

Non-ICU inpatients are treated with a respiratory fluoroquinolone **or**, alternately, an IV or oral β -lactam

plus either a macrolide **or** doxycycline. Start treatment **immediately** once you determine admission is necessary.

Inpatients — ICU

ICU patients (with no risk factors for *Pseudomonas*) are treated with a β -lactam **plus** either a respiratory fluoroquinolone **or** a macrolide. If the ICU patient has risk factors for *P. aeruginosa*, start with 2 anti-pseudomonal drugs. If CA-MRSA is suspected based on historical risk factors, add linezolid or vancomycin. Start treatment immediately.

Narrowing Empiric Therapy

By day 3, you will know whether your patient is improving, and you might have an organism identified if you sent any specimens for microbiology (sputum and blood cultures, urine antigen tests).

Switch to oral meds if your patient is improved with stable blood pressure and can take drugs by mouth. If the lab identifies a bug, narrow treatment to focus on that organism.

Treatment varies from 5 days (clear cut, improving cases) to 14 days (extensive pneumonias). Follow up with a chest x-ray about 4–6 weeks after discharge, and consider malignancy in the patient whose lung has persistent abnormalities.

If your patient deteriorates over the first 3 days on empiric treatment, think of these possibilities:

- Maybe you have the **wrong diagnosis**, and it is not an infectious infiltrate; e.g., PE, CHF, connective tissue disease, hypersensitivity pneumonitis.
- Maybe your empiric regimen is **not covering** the causative organism (either you missed covering the bug or the bug is resistant). Revisit that list of risk factors and associations. What did you miss? If you are giving the right drugs, are you giving the correct doses?
- Maybe there is a **new infection**, in addition to the original one; e.g., staph pneumonia in addition to original viral pneumonia. Think empyema if a parapneumonic effusion was present on admission. Chest x-rays that demonstrate development of pneumatoceles or lung abscesses over the first few days should make you think pneumococcus, CA-MRSA, and *Pseudomonas*.

Now let's talk about the individual organisms that cause CAP. Some of this information has been briefly covered before, but a focused discussion is necessary.

“TYPICAL” ORGANISMS OF CAP

Streptococcus pneumoniae

Pneumococci live in the nose and throat of up to 40% of healthy children. Any adult who has contact with children, day care centers, and other crowded conditions

Quick Quiz

- A patient who works on an animal farm develops pneumonia. What organism should you think about?
- What organism should you consider if pneumonia develops in a patient who spent an afternoon in a bat cave in Mississippi?
- What organism should you think about if pneumonia develops in a patient who drove through an Arizona dust storm?
- What organism should you consider if a chronic, cavitating pneumonia develops in a male logger from Arkansas?
- Name 2 drugs that are recommended to treat outpatient CAP in patients without risk factors for DRSP.
- Name 2 regimens recommended to treat inpatient CAP in the non-ICU patient.
- What antibiotics would you use for empiric treatment of the ICU patient with cavitary pneumonia and risk factors for *S. aureus*?
- What are the diagnostic possibilities for the unresponsive patient with apparent pneumonia?
- Name some potential pulmonary complications of pneumococcal pneumonia.
- Describe the patients who should be vaccinated with PPSV23.

(military barracks, dormitories, homeless shelters, prisons) is at risk for becoming colonized and subsequently infected.

Children who receive frequent antibiotic prescriptions for viral illnesses are a source of drug-resistant strains because the colonizing organisms mutate under the drug pressure. Upper respiratory inflammation from a cold virus, in the colonized patient, then sets the stage for bacterial pneumonia and/or sinusitis.

Patients most at risk for pneumococcal disease are > 65 years of age or have comorbidities (e.g., diabetes, alcoholism, and lung, heart, or renal disease). Asplenic patients (e.g., sickle cell) and patients with humoral immunodeficiencies (e.g., AIDS, myeloma, CLL, lymphoma) are especially at risk because pneumococci are encapsulated.

To review: DRSP is associated with age $\geq$ 65 years, recent β -lactam therapy, alcoholism, immunosuppression, multiple comorbidities, and exposure to child in day care.

In addition to generic signs and symptoms of pneumonia, think pneumococcus if your at-risk patient presents with shaking chills, pleuritic chest pain, and “rust-colored

sputum”. CBC reveals a high WBC count. (Leukopenia is associated with mortality.) Chest x-ray often shows **lobar consolidation** (Image 3-15). If sputum is sent for microbiology, suspect pneumococcus when the Gram stain result describes intracellular, lancet-shaped gram-positive diplococci. (Again, do not be fooled by the slide with many epithelial cells; this is just spit, and non-diagnostic, no matter what else you may see on it.) Blood cultures are positive in 25% of hospitalized cases of pneumococcal pneumonia.

Look out for these complications: lung abscess, pneumatoceles, and empyema in the patient with history of parapneumonic effusion.

Know that multilobar disease, bacteremia, and peripheral blood WBC < 6,000/ μ L are associated with increased mortality.

Diagnosis of *S. pneumoniae* pneumonia is supported when a good quality sputum Gram stain identifies the **lancet-shaped gram-positive diplococci**, and the organism is identified in sputum culture. A positive blood culture and/or pneumococcal urinary antigen test are diagnostic.

Treatment: For susceptible pneumococcus, **many drugs** are effective, including tetracyclines, macrolides, penicillin, cephalosporins, and respiratory quinolones. Don't forget about the evolving resistance.

DRSP strains are treated with a cephalosporin with known activity against DRSP, a respiratory quinolone, or with higher doses of a β -lactam (with hopes of overcoming the resistance—a useful strategy if the infection is not severe).

There are 3 vaccines now licensed for pneumococcal disease: the 23-valent polysaccharide vaccine (PPSV23, contains 23 prevalent serotypes), the 7-valent protein conjugate vaccine (PCV7, contains 7 prevalent serotypes), and the most recent 13-valent protein conjugate vaccine (PCV13, contains 13 serotypes).

Adults are given PPSV23 if they are > 65 years of age, are cigarette smokers, have a chronic disease (HF,

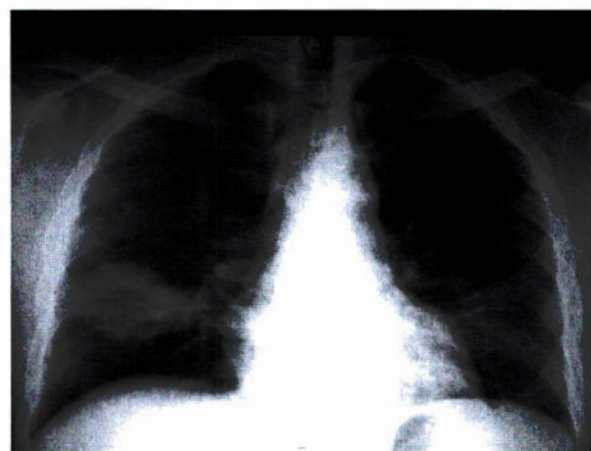


Image 3-15: Round pneumonia (often seen in pneumococcal pneumonia)

COPD, asthma, DM, cirrhosis), are functionally or anatomically asplenic, or are immunosuppressed. Many patients with comorbidities (i.e., those who need the vaccine most) do not develop an adequate antibody response. Current recommendations include a **booster** vaccine for patients over 65 years of age if **> 5** years have elapsed since initial vaccination.

PCV7 and PCV13 are approved for use in children **< 2** years of age because the protein conjugate is more effective at stimulating the immune system in this age group. PCV7 has dramatically reduced the incidence of invasive pneumococcal disease in children (which subsequently **confers reduction** in disease in adults). We are now seeing emergence of invasive disease caused by the less common serotypes not included in PCV7. This “replacement phenomenon” is most often mediated by capsular switching. Thus, PCV13 has been manufactured to include most of the circulating serotypes. PCV13 is intended to replace PCV7 in practice.

Haemophilus influenzae

Haemophilus influenzae may be encapsulated or unencapsulated (“nontypeable”). Because of widespread use of the Hib vaccination, most *H. influenzae* infections in the U.S. are nontypeable, caused by invasion of the bacteria across mucous membranes. Pneumonia from nontypeable strains is most often seen in patients with underlying lung disease (COPD) and AIDS.

Diagnosis: This pneumonia presents generically with fever, cough, and dyspnea. A good sputum sample often shows you the organism on Gram stain: pleomorphic gram-negative coccobacilli. Definitive diagnosis is made when you grow the organism in culture from a normally sterile site (e.g., pleural fluid or blood—both uncommon).

Treatment: Antibiotics effective against *H. influenzae* are ampicillin (or AM-CL if resistance is suspected or common in your area), 3rd generation cephalosporins, doxycycline, fluoroquinolones, and TMP/SMX.

Staphylococcus aureus

S. aureus colonizes the anterior nares and gets distributed to the skin with fingers. Regular staph strains don’t cause problems in immunocompetent patients without **skin breaks**. But if the immune system or skin barrier breaks down, the staph can cause a problem.

Also, there are much stronger strains. A Panton-Valentine leukocidin producing strain (PVL-SA) can cause a virulent necrotizing CA-MRSA in immunocompetent patients.

Staph species can be either susceptible to methicillin (and subsequently other β -lactams) or resistant to methicillin (MRSA, a surrogate marker for resistance to all β -lactam drugs).

Lastly, staph can be categorized by whether the strain is hospital-acquired (HCAP or HAP) or community-acquired (CAP)—generally predicted based on the patient’s history, the organism’s antimicrobial susceptibility, and toxin analysis.

Staphylococcus aureus CAP is usually seen in patients with a preceding **influenza** infection (as a suprainfection), although *de novo* pneumonia due to CA-MRSA is being seen more frequently.

Presentation is typical for pneumonia with fever, dyspnea, and cough; but patients with staph may have hemoptysis with “**salmon pink**” sputum, and diffuse lung infiltrates and/or pneumatoceles.

Think suprainfection with *S. aureus* if the history is consistent with resolving **influenza** that worsens with new symptoms of dyspnea and cough.

Think CA-MRSA in cases of severe pneumonia with pink sputum and pneumatoceles in an immunocompetent patient with a history of close contact with others or poor hygiene.

Diagnosis: As with other pneumonias, diagnosis is supported when a good sputum sample shows the organism on Gram stain (gram-positive cocci in clusters) and grows the organism in culture. Blood cultures are helpful if positive, but they are usually not.

Complications include empyema (frequent), an immune-complex type of glomerulonephritis, and pericarditis.

Treatment: **Methicillin-sensitive** *S. aureus* pneumonia can be treated with a β -lactam—nafcillin is usually the drug of choice.

MRSA pneumonia should be treated with either vancomycin or linezolid. Daptomycin is **ineffective** for respiratory infections; do **not** use it to treat staph pneumonia!

CA-MRSA strains often have preserved susceptibility to TMP/SMX, quinolones, and clindamycin. These drugs are fine to use in treating skin infections with CA-MRSA but not lung infections. Use vancomycin or linezolid for serious MRSA lung infections.

Klebsiella

The major CAP-causing enteric gram-negative organism is *Klebsiella pneumoniae*, which colonizes the oropharynx of alcoholics and patients with uncontrolled lung disease or diabetes. It is an uncommon cause of CAP.

Klebsiella CAP presents with typical features of pneumonia (cough, dyspnea, fever). As the pneumonia worsens, the lung can become necrotic, and patients get sicker. Be aware of some buzzwords classically associated with gram-negative pneumonia: “**currant jelly** sputum” (bloody sputum that resembles jelly) and the “**bulging fissure** sign” (an x-ray finding in *Klebsiella* pneumonia that is associated with a lobar infiltrate).

Quick Quiz

- Name some potential complications of staph pneumonia.
- What drug choices are available for targeted treatment of *S. aureus* pneumonia?
- The “bulging fissure sign” is associated with what organism that causes pneumonia?
- What is an acceptable regimen for empiric treatment of pneumonia in the ICU patient with risk factors for *Pseudomonas*?
- Describe the microbiologic characteristics of *Moraxella*.

Diagnosis is made via Gram stain and culture of sputum and blood (usually performed because the patient with gram-negative pneumonia often presents with severe disease and may end up in the ICU).

Treatment: Know that many enteric gram negatives are either innately resistant to ampicillin or have acquired ampicillin resistance. When you suspect gram-negative pneumonia, your empiric antibiotic choice should be broad in spectrum; i.e., an extended-spectrum penicillin with a β -lactamase inhibitor, such as piperacillin-tazobactam (because you need coverage for gram-positive organisms also, until the lab identifies an organism for you). Once cultures identify your organism, you can narrow treatment based on resistance testing—often an oral quinolone is adequate to finish therapy.

Pseudomonas aeruginosa

Pseudomonas grows in **moist** environments. Patients who are infected with this organism in their lungs have an **underlying illness** that allows their alveoli and airways to stay moist. And most often, the underlying disease process requires either chronic or intermittent antibiotic use, such that drug pressure selects for colonization with resistant and hearty gram negatives.

So *Pseudomonas* causes CAP in patients with underlying lung disease, especially cystic fibrosis, bronchiectasis, and in patients who use steroids or antibiotics frequently.

Patients without lung disease who inhale a large amount of steam from **hot tubs** that are heavily contaminated with *Pseudomonas* can also present with pseudomonal CAP. *Pseudomonas* is not a common cause of CAP—more often it causes HCAP.

Presentation is typical with cough, dyspnea, and fever. The patients with chronic lung disease usually look sicker, though, because this bug is bad and they don't have much reserve.

Diagnosis of *Pseudomonas* pneumonia is trickier than with other causes of CAP because the organism is **harder**

to find. A sputum Gram stain with many polys + sputum culture that grows the organism suggests infection. Of course, it takes a while for the culture to grow, so you have to have a high index of suspicion for this bug and treat empirically.

Treatment: If you suspect *Pseudomonas* based on underlying chronic disease or hot tub exposure, empiric treatment should include **2 antipseudomonal drugs**—1 of which should be a broad-spectrum **antipseudomonal penicillin** (e.g., piperacillin-tazobactam, ticarcillin-clavulanic acid, or imipenem-cilastatin). **Ciprofloxacin or an aminoglycoside** can be added as the 2nd drug. Once culture results are available, with susceptibility results, the regimen can be narrowed.

For all of the above organisms, it is important to know which organisms are common in your area and your local antibiotic resistance patterns as you make decisions on empiric therapy. This information is available to you from your hospital microbiology lab in the form of an “antibiogram.”

Moraxella catarrhalis

Moraxella catarrhalis colonizes the mouth and upper airway of both children and adults and is a frequent cause of otitis and sinusitis. Importantly, however, this organism causes CAP only in patients with underlying lung disease, usually **COPD**. In 1 large study, *Moraxella* never caused pneumonia in healthy individuals. CAP from this organism indicates severe lung disease, as 50% of patients die from their disease within 3 months of infection.

Moraxella CAP is slightly less acute than disease caused by pneumococcus or *H. influenzae*. Symptoms are less severe. The x-ray pattern is variable, ranging from lobar infiltrates to diffuse involvement, and even interstitial disease in some cases.

Diagnosis is usually simple because a quality sputum sample shows an overwhelming number of obvious organisms that are described as **gram-negative cocci**. It is useful to look at the Gram stain yourself because the organisms line up side-by-side and look like a pair of kidneys (not usually reported by the micro tech on the Gram stain result).

Treatment is straightforward because the bug is generally susceptible to most drugs used to treat pneumonia: doxycycline, macrolides, cephalosporins, or amoxicillin/clavulanic acid. Up to 90% of isolates produce a **β -lactamase**, which breaks down penicillins but not cephalosporins.

“ATYPICAL” ORGANISMS OF CAP

Recall, these organisms are defined as “atypical” because they are not identifiable by Gram stain or routine bacterial culture, and they are resistant to β -lactam antibiotics. These organisms require special culture media +/- serologic tests to establish diagnosis.

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of CAP in **young** patients. Incubation is 2–3 weeks, and onset of dyspnea, cough, and fever is typically insidious, although occasionally presentation can mimic pneumococcal disease. Extrapulmonary manifestations of *Mycoplasma* infection include hemolytic anemia, splenomegaly, erythema multiforme (and Stevens-Johnson syndrome), arthritis, myringitis bullosa, pharyngitis, tonsillitis, and neurologic changes—especially **confusion**.

Diagnosis is made by measuring acute and convalescent IgM antibody titers using enzyme immunoassay. If the convalescent titer rises by $\geq 4\times$ the acute titer, then you can make the diagnosis retrospectively with $> 95\%$ sensitivity and specificity.

Cold agglutinins are nonspecific IgM antibodies that support the diagnosis in settings of high clinical suspicion but have low sensitivity and specificity.

Treatment of *Mycoplasma pneumoniae* is a macrolide—or doxycycline if the macrolide is not tolerated. Patients sometimes take a long time (> 6 months) to fully recover!

***Chlamydia pneumoniae* (TWAR)**

Chlamydia pneumoniae (formerly *Chlamydia*) more commonly causes CAP in adults > 65 years of age.

Symptoms are similar to *Mycoplasma pneumoniae* with the addition of **pharyngitis** and **hoarseness**. Often, there is a biphasic illness; the patient presents with a sore throat that is negative for group A strep; then 2–3 weeks later, hoarseness and pneumonia develop. Again: sore throat $\rightarrow$ pneumonia + hoarseness = TWAR.

Diagnosis of pneumonia due to *Chlamydia pneumoniae* is confirmed by measuring acute and convalescent IgM and IgG titers using microimmunofluorescence or complement fixation; antigen detection using ELISA tests; or, PCR of respiratory secretions. The first 2 are most useful clinically.

Treatment: Effective antibiotic therapy includes doxycycline or macrolides for 3 weeks.

Legionella pneumophila

Legionella pneumophila causes CAP when the organism is inhaled from a contaminated water supply. Epidemics are seen in hotels and on cruise ships, and the organism can also cause HAP when hospital water systems are contaminated.

Presentation can be similar to, and is often confused with, *Mycoplasma pneumoniae*. The disease begins with headache, GI symptoms (especially diarrhea), and occasionally confusion, then evolves into lung-related symptoms of cough and dyspnea.

Labs can show hyponatremia, hypophosphatemia, thrombocytopenia, and elevated lactate dehydrogenase and C-reactive protein.

When you see multisystem disease, think *Legionella*! Also think *Legionella* in the patient who is admitted for typical CAP but fails to improve on empiric therapy.

Diagnosis: Preferred diagnostic tests for *Legionella pneumophila* pneumonia are sputum culture on special media (buffered charcoal yeast extract agar, but results take longer than 3 days) and the urinary antigen test using enzyme immunoassay. The urinary antigen assay is less sensitive with milder disease.

Treatment: macrolides—especially azithromycin or quinolones. If severely ill, add rifampin as initial treatment.

Endemic Fungi

Coccidioides immitis

Coccidioides immitis infection (coccidioidomycosis) is endemic in the Southwestern U.S., especially Arizona and California's San Joaquin valley.

Typical history includes recent travel to Arizona and “got caught in a dust storm.” Soon after, the patient develops fatigue, fever, and arthralgias. The resulting illness can be subclinical and self-resolve, or CAP can develop within 2–3 weeks of exposure. The fatigue and arthralgias can linger; thus, infection has been termed “desert rheumatism.”

Erythema **nodosum** and erythema **multiforme** are associated skin findings.

Chest x-ray findings are variable from no changes to adenopathy, infiltrates, nodules, and thin-walled cavities that can persist.

Disseminated coccidioidomycosis is seen in immunocompromised/HIV. This is a fulminant disease with meningitis and skin and bone involvement. Even with treatment (amphotericin B), it is frequently fatal.

Diagnose by isolating the organism using KOH smears and fungal cultures of sputum and identifying serum antibody using immunodiffusion.

Treatment of coccidioidomycosis: The common, **self-limited** form usually does not require treatment and may leave thin-walled lung cavities.

Treat with fluconazole or itraconazole. Use amphotericin B if there is hemoptysis or enlargement on chest x-ray.

Histoplasma capsulatum

Histoplasmosis is uncommon, except in endemic areas of the southern and midwestern U.S. It is especially seen in the Mississippi and Ohio River valleys (but do not confuse this with San Joaquin Valley Fever above).

Think of “histoplas**MO**sis” (Mississippi, Ohio). It is associated with soil animals (chickens) and cave-dwelling animals, such as bats.

Quick Quiz

- What are the extrapulmonary manifestations of infection with *Mycoplasma pneumoniae*?
- Pneumonia caused by *C. pneumoniae* (TWAR) is associated with one unusual symptom. What is it?
- Pneumonia in a patient with associated mental status changes and diarrhea should make you think of what organism?
- Your patient returns from a trip to the southwest U.S. and comes to you with erythema nodosum. What fungus do you include in your differential?
- Which endemic fungus causes hilar adenopathy, focal alveolar infiltrates, and multiple lung nodules?
- Describe the microbiologic characteristics of *Blastomyces*.
- Which patients are at increased risk for complications from infection with novel H1N1?

With acute disease, the chest x-ray shows hilar adenopathy and focal alveolar infiltrates. Heavy exposure (“epidemic,” disseminating form) is suggested by a chest x-ray revealing **multiple nodules** in addition to the hilar adenopathy.

Diagnose histoplasmosis:

- If systemic disease, use antigen test of the blood, BAL, or urine.
- If **pneumonia**, use serologic tests. Complement fixation is more sensitive than immunodiffusion.

No treatment is indicated for the usual disease, although some recommend itraconazole.

Disseminated disease requires amphotericin B (usually liposomal because it gets into the lymph nodes, spleen, and marrow better—this is where histo usually replicates most). HIV patients require chronic suppression with itraconazole.

Blastomyces dermatitidis

Blastomycosis is uncommon. It is usually acquired by middle-aged men in the central, southeast, and mid-Atlantic states. (Think of having a “blast” in Chicago.) M:F is 10:1!

Progression can be indolent to severe.

Chest x-ray shows mass-like infiltrates.

Diagnosis of blastomycosis: **No** skin test is available. Blastomycosis is more pyogenic than the others, and patients can cough up purulent sputum that reveals the organism with **KOH** prep. Buzz phrase for blasto is “**broad-base, budding yeasts**” (Image 3-16).

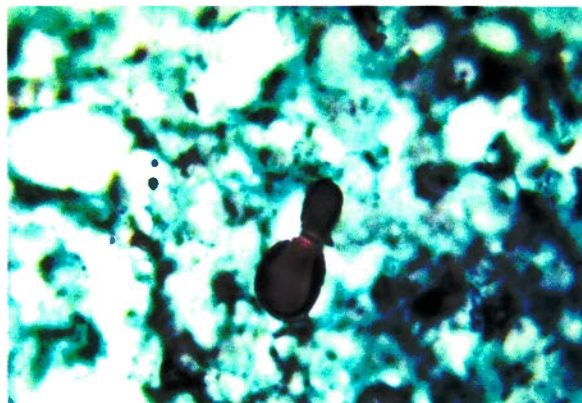


Image 3-16: Methenamine silver stain of pathology specimen shows the broad-base budding of blasto yeasts

Treatment of blastomycosis:

- Indolent: observe or oral itraconazole.
- Mild-to-moderate: itraconazole x 6 months; also can use ketoconazole or fluconazole.
- Severe: amphotericin B; then may switch to itraconazole. HIV patients require chronic suppression with itraconazole (as with histoplasmosis, previous).

Viruses

Influenza

Influenza A (common subtypes: H3N2, seasonal H1N1, and novel H1N1 [2009 “swine flu”]) and **B** viruses can cause primary viral pneumonia or be associated with secondary bacterial suprainfection. Lung secretions grow the virus in culture.

Think **primary viral** pneumonia in a patient who has typical influenza symptoms with progressive worsening of cough and dyspnea. Exam is typical for pneumonia but with scant sputum production. Hypoxemia is common. In the 2009–2010 novel H1N1 influenza A pandemic, viral pneumonia was most common in young people and pregnant women.

Think **secondary bacterial** pneumonia as an influenza complication in the patient whose flu appears to be improving then suddenly worsens with signs of pneumonia (cough, dyspnea, and new fever). Think *S. aureus*, pneumococcus, and *H. influenzae*. Gram stain and culture of sputum usually show the suprainfecting organism.

More common than either of the above presentations is the **mixed viral and bacterial** pneumonia seen with influenza outbreaks. This is the patient who gets influenza and then eventually gets associated bacterial pneumonia, but time does not lapse between obvious flu and pneumonia—rather the clinical picture is one of blended disease. In this situation, the patient coughs up purulent sputum after a few days of influenza illness, then waxes and wanes between improvement and exacerbation. X-rays show areas of consolidation, and sputum may show an abundance of bacteria.

Diagnose influenza A and B with rapid antigen detection assay—especially recommended is an assay that distinguishes between influenza A and B. The rapid tests are not 100% sensitive, however, and false negatives are common. Subtyping analysis requires PCR testing and is done only at specialized labs.

Treatment: Primary prophylaxis is recommended for exposed individuals in nursing homes and in those with chronic diseases. Empiric treatment of influenza requires use of **zanamivir** (Relenza®) or **oseltamivir** (Tamiflu®) because most cases of influenza A/H3N2 have acquired **resistance** to amantadine and rimantadine. (Influenza B is inherently resistant to amantadine and rimantadine.) Some H3N2 and seasonal H1N1 subtypes of influenza A even have resistance to oseltamivir, but novel H1N1 (swine flu) remains susceptible.

Adenovirus

Adenovirus in adults initially causes cold symptoms (sore throat, runny nose, and cough) with eventual development of pneumonia in a small subset. Most cases of adenovirus pneumonia have been observed in the enlisted military.

Immunodeficient patients can develop life-threatening pneumonia from adenovirus.

Diagnostics are not usually done except in immunosuppressed patients (culture on respiratory secretions and PCR testing).

Treatment is supportive.

RSV

Respiratory syncytial virus usually causes only a cold in adults, but the elderly and patients with immunosuppression can get pneumonia. Diagnosis can be made using a rapid test on respiratory secretions. Treatment is supportive.

VAP, HAP, and HCAP

Overview

The following is according to 2005 ATS/IDSA guidelines on hospital-acquired pneumonia.

VAP (ventilator-associated pneumonia) is defined as pneumonia that develops ≥ 48 –72 hours after intubation.

HAP (hospital-acquired pneumonia) is defined as pneumonia that develops 48 hours after admission to hospital. So you can see that VAP is actually a type of HAP. But for distinction and clarity (and according to the 2005 guidelines), we will treat VAP separately.

HCAP (health care-associated pneumonia) is defined as pneumonia in a patient who is **not** currently hospitalized but has had extensive “**health care contact**”; e.g., IV antibiotics or chemo or wound care in last month; lives

in a nursing home; hospitalized more than 2 days in the last 3 months; or went to hospital or dialysis clinics for services within past month.

These 3 types of pneumonia are part of the same spectrum of disease, with the **common concern** that they are more likely than CAP to have multidrug-resistant (**MDR**) organisms.

Ventilator-Associated Pneumonia (VAP)

The organisms that cause VAP vary depending on how soon after admission patients are intubated.

VAP in patients intubated within 1–4 days of admission is more likely to be caused by **CAP** organisms—and less likely to be drug-resistant.

The more time elapsed (usually > 5 days) since admission before intubation, the more likely they are to develop pneumonia from **hospital organisms** that have colonized the oropharynx and upper airways—organisms that tend to be multidrug resistant (**MDR**).

The most commonly encountered VAP MDR infections are:

- MRSA
- *Pseudomonas* species
- *Stenotrophomonas maltophilia*
- *Acinetobacter* species

Any patient who develops new fever or clinical deterioration while on a ventilator should be suspected of having pneumonia. Incidence is highest in the first 5 days of ventilator use. **Malnutrition** in the ICU is an important predisposing condition.

For diagnostics, the best samples to get for culture are the deepest; e.g., protected specimen brush samples using a bronchoscope (as opposed to endotracheal aspirates) because they are less likely to be contaminated by colonizing flora.

Quantitative cultures are often used to help differentiate contaminated culture material from true infection. A threshold for culture growth is accepted for each type of specimen; when growth exceeds the threshold, pneumonia is considered present (e.g., endotracheal aspirate diagnostic threshold = 10^6 cfu/mL; protected brushings diagnostic threshold = 10^3 cfu/mL).

Treatment of VAP relies very much on results of culture to guide decisions based on local resistance patterns.

For empiric treatment of VAP:

- If the patient was recently admitted, treat for CAP organisms per [Figure 3-7](#) on [page 3-46](#).
- If the patient has risk factors for MDR gram negatives, then empiric treatment is begun with 3 antibiotics—2 effective antipseudomonal drugs and vancomycin or linezolid for MRSA (once specimens are obtained).

Quick Quiz

- Name the drug options for empiric treatment of influenza.
- What organisms are the usual causes when a patient requires intubation, and then develops pneumonia within the first couple of days after admission?
- Characterize the organisms that cause pneumonia in patients who have been in the ICU on the ventilator for more than 5 days.
- Describe the presentation of the patient with aspiration pneumonia. With lung abscess?

Note: As these terms are currently defined, patients who are admitted **with** pneumonia and then intubated do **not** have VAP. They have severe **CAP or HCAP**.

By definition, VAP is pneumonia that develops $\geq 48-72$ hours **after** intubation. Remember that CAP organisms can be MDR; they are just less likely to be. Patients intubated for severe CAP are likely to have pneumonia caused by: pneumococcus, *Haemophilus*, CA-MRSA, *Klebsiella*, *Pseudomonas*, *Mycoplasma*, *Moraxella*, *Legionella*, or viruses.

Hospital-Acquired Pneumonia (HAP)

HAP (non-VAP) is not much different from VAP, except that patients are not on a ventilator. The organisms are much the **same**, except MDR organisms are less frequently involved, and patients are less sick.

Health Care-Associated Pneumonia

HCAP is similar to HAP and is treated the same. Note that HCAP patients are more likely to have MDR organisms when **first** evaluated, whereas HAP and VAP usually won't get an MDR pneumonia caused by hospital organisms until > 5 days after admission.

Note: Regarding the 2010 HCAP/HAP/VAP guidelines, it appears that you will see the terminology change somewhat. It is probable that HAP and VAP will be defined as subsets of HCAP.

The non-changing, important point is highlighted above and again repeated here: The cause of pneumonia occurring 1–4 days after admission is likely to follow the spectrum seen with CAP; > 5 days after, more likely to be hospital-acquired organisms.

ASPIRATION SYNDROMES

With aspiration syndromes, infection usually occurs only after a **large amount** of material is aspirated; e.g., after endotracheal intubation, seizures, or in a severely

intoxicated patient. The infiltrate usually occurs in the RLL. When a patient aspirates, it is not necessary to start antibiotics immediately because stomach contents often cause only a chemical pneumonitis.

Even so, observe the patient carefully because cavitating pneumonia and/or empyema can develop. The breath can be horrendously malodorous in those with anaerobic infection! Most common infection-causing bacteria are *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, and anaerobic streptococci.

Diagnosis is usually clinical, based on history of aspiration. Radiograph shows an infiltrate, possibly organizing into a cavity (**Image 3-17** and **Image 3-18**). Gram stain shows **mixed** flora. Sputum is unreliable.

Treatment: The antibiotic used for aspiration pneumonia must cover above-the-diaphragm **anaerobes** (i.e., not metronidazole), which usually are the cause of **cavitation**. A β -lactam + β -lactamase inhibitor (AM-CL or AMP-sulbactam) or clindamycin is generally recommended.

LUNG ABSCESS

A lung abscess forms after an infection causes necrotic lung to cavitate. The most common cause is **aspiration** of organisms from the oropharynx. Risk factors for aspiration include seizures, alcoholism, esophageal abnormalities, and swallowing problems. Typical organisms that live in the mouth are anaerobes, but alcoholics have a high incidence of gram-negative enterics (e.g., *Klebsiella*).

Lung abscess as a focus of metastatic infection can occur with **right-sided** staph endocarditis in injection drug abusers and in dialysis and chemo patients who have **chronic** venous access.

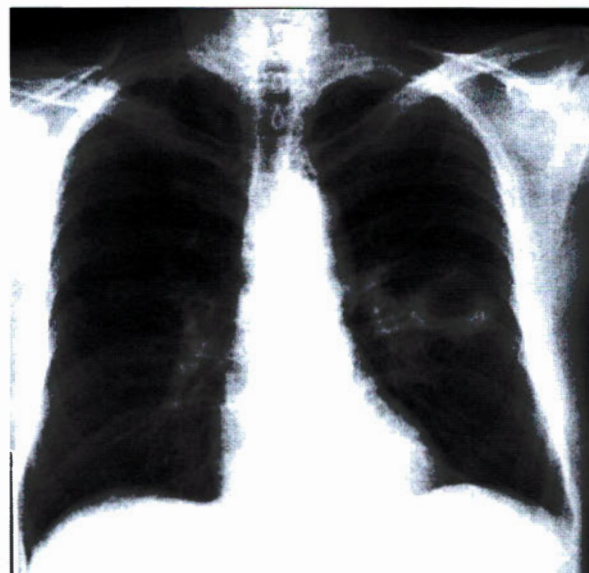


Image 3-17: Cavitory pneumonia from aspiration

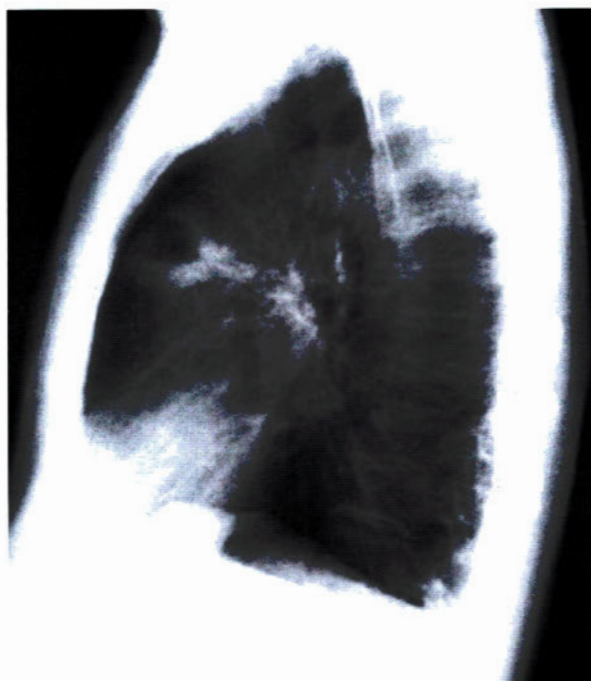


Image 3-18: Cavitary pneumonia from aspiration

Abscesses present as an indolent cough with purulent, often fetid, sputum (especially in anaerobic infections), although abscesses due to metastatic staph are more acute. The chest x-ray usually shows cavitary lesions (in the upper lobes and posterior segment of the lower lobes in cases of aspiration).

Diagnosis is usually clinical (need to exclude TB) because anaerobes are particularly difficult to culture.

Treatment with clindamycin is preferred over β -lactams because mouth anaerobes often make β -lactamases. Again, don't use metronidazole for anaerobic infections above the diaphragm! If gram-negative organisms are suspected, use a **combination** β -lactam/ β -lactamase inhibitor drug, such as ampicillin-clavulanic acid.

MYCOBACTERIAL INFECTION

TUBERCULOSIS

Overview

Much of the following on tuberculosis (TB) is adapted from the CDC/ATS statements. You can download them from <http://www.cdc.gov/tb/>.

TB is a favorite Board topic. For good reason—the incidence of TB began increasing after 1988. This is mainly due to TB associated with HIV infections.

Not much yellow highlighting will be shown here because you must **know** this entire section perfectly!

The TB infection sequence goes: **primary** infection → **latent** infection → **reactivation**:

Primary tuberculosis occurs when aerosolized, contaminated droplets are inhaled and droplet nuclei reach

the alveoli, where bacteria multiply locally for a while and then spread to areas of the body with high oxygen tension (bone, brain, kidneys, apices of lungs). Cell-mediated immunity kicks in to arrest dissemination and growth of organisms during this initial stage. Patients who do not have functional **cell-mediated** immunity can develop active tuberculosis during this phase—termed “**primary TB**.” Disease occurs throughout the lungs or in the sites of dissemination (e.g., meningitis), and symptoms manifest quickly after initial exposure. **Children** and **AIDS** patients are most at risk for primary disease.

Latent: In the exposed patient with a **functional** immune system, the organisms are held at bay by the formation of granulomas (and the patient does not develop primary infection). In the lung, the granulomas sometimes calcify and can be observed as **Ghon complexes**. Usually this sensitized person will have no evidence of disease—but a TB skin test will react, showing that he is infected with organisms. A significantly reactive TB skin test in a patient with no evidence of active tuberculosis is called “latent TB infection” (**LTBI**).

Reactivation: With aging and development of comorbidities, the cell-mediated immune system sometimes loses its ability to keep the organisms in check, and the patient develops “reactivation TB.” Reactivation disease occurs at the sites of initial dissemination (lung apices, brain, kidney, bones). The risk of reaction is highest after exposure (5% within first 2 years and another 5% thereafter; HIV/AIDS patients are an exception and have **40%** risk of reactivation within **months**).

Common presenting signs of reactivation tuberculosis include fever, weakness, night sweats, and weight loss. Pulmonary disease is indicated by cough, pleuritic chest pain, and hemoptysis.

The chest x-ray may show an upper lobe infiltrate and hilar lymphadenopathy (**Image 3-19** and **Image 3-20**). Patients who develop **cavities** have the largest burden of organisms.

Most reactivation tuberculosis is pulmonary; 15% is extrapulmonary. Consider TB in a patient with indolent, chronic arthritis or chronic meningitis.

Miliary tuberculosis is the term given to uncontrolled hematogenous spread of *M. tuberculosis*. The clinical picture is variable—from overwhelming disease with multisystem organ failure (in primary infection) to chronic wasting (in reactivation infection). The classic chest x-ray is a faint and diffuse reticulonodular infiltrate (**Image 3-21**).

Diagnosis. The CDC-recommended approach to diagnose active pulmonary TB includes:

- TB skin test or interferon gamma release assay (IGRA)
- Chest x-ray
- Acid-fast smears and cultures of the sputum
- At least 1 nucleic acid amplification test (NAA; PCR)

Quick Quiz

- Describe the differences between primary TB, latent TB, and reactivation TB.
- How do you make the diagnosis of active pulmonary TB?

Acid-fast bacteria (AFB) smears are cheap but are only ~ 80% sensitive (false negatives) and have a 50–80% positive predictive value (the AFB could be non-tuberculous mycobacteria [NTM]—you don't know until you get the organism precisely identified). Some of these issues are resolved with mycobacterial cultures, but they take a long time to grow.

NAA tests can be done on both smear-positive and smear-negative sputum samples and improve both sensitivity (to ~ 95%) and positive predictive value (because the PCR can distinguish between TB and NTM).

Do **not** wait for test results to start treating reactivation TB if your clinical suspicion for disease is high; i.e., positive TB skin test or IGRA and risk factors.

Report all persons with current reactivation tuberculosis or suspected current reactivation tuberculosis to the state or local health department.

We will cover treatment of LTBI and active TB after we discuss screening for LTBI.

Screening for Latent TB Infection (LTBI)

Who gets screened?

High-risk groups including:

- HIV or high-risk for HIV
- Close contacts of those with reactivation tuberculosis
- IV drug abusers
- Low-income, medically underserved populations
- Homeless



Image 3-19: RUL pneumonia, consistent with TB (non-cavitary)

- Migrant workers
- Residents of long-term care facilities (nursing homes and jails)

How are they screened?

3 methods:

- 1) The **tuberculin skin test** is the best and most widely used.
- 2) Many centers now are using the **IGRAs**.
- 3) For people easily **lost to follow-up**, such as in some jails and homeless shelters, screen for actual disease (chest x-ray and sputum for AFB)—or use the IGRA.

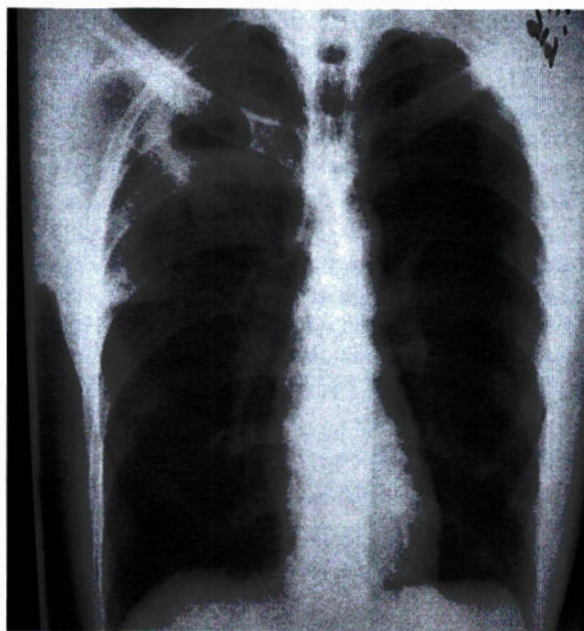


Image 3-20: Reactivation TB with RUL cavitary lesion

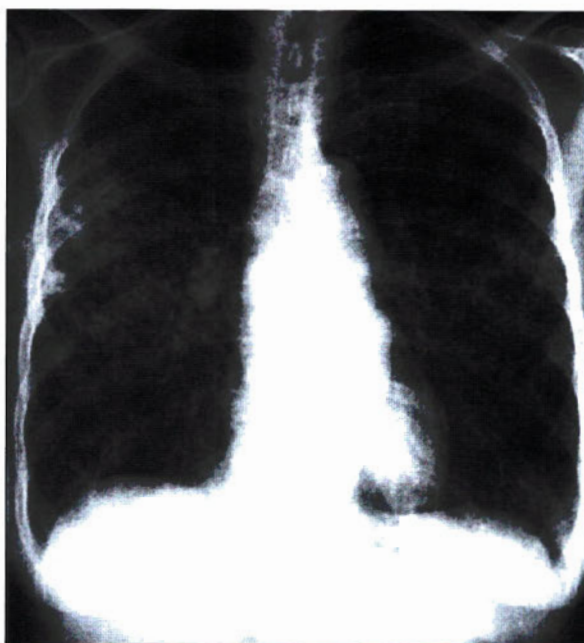


Image 3-21: Miliary tuberculosis

Tuberculin skin tests react in most **infected** people. Having said that, know that **25%** of patients with active pulmonary TB have **non-reactive TB skin tests**. So, a negative TB skin test does not exclude TB in patients who have high pretest probabilities of disease. The tuberculin skin test is contraindicated **only** if there has been a necrotic skin reaction to previous tests.

TB skin test may be given if the patient has had the **BCG** vaccine (used in some countries as a TB vaccine). Because most of these people were vaccinated as infants, the PPD result will probably be **valid** and should be interpreted in the **standard** fashion and treated accordingly.

The standard Mantoux test is an intradermal injection of 0.1 mL (5 tuberculin units) of purified protein derivative (PPD) tuberculin in the forearm. The injection site is evaluated **48–72** hours after the injection. The reading is based on the diameter of the **indurated**/swollen area—not the erythematous area—measured perpendicular to the long axis of the forearm (*Image 3-22*).

The current recommendations from the CDC as to what constitutes a significant reading take into account the degree of clinical suspicion of LTBI. The following list shows how a particular diameter of induration may be significant in one group and insignificant in another.

All of the following are considered significant (i.e., should be treated) skin tests:

≥ 5 mm is significant for those in the high-risk group:

- **HIV** or major cell-mediated dysfunction
- Fibrotic changes on chest x-ray consistent with prior TB
- **Close contact** with a documented case
- Patients with organ transplants and other immunosuppressed patients (**receiving the equivalent of ≥ 15 mg/d of prednisone** for 1 month or more, or receiving TNF-inhibitor or chemotherapy)

≥ 10 mm is significant for those in the intermediate-risk group:

- Homeless persons
- Recent immigrants (within 5 years) from high-prevalence countries
- Injection drug users who are HIV-negative
- Prisoners
- Health care workers!
- Nursing home patients and staff
- Patients with diabetes, silicosis, malignancy, and malnutrition
- “New converters” (discussed next)

≥ 15 mm is significant for the low-risk group. This includes most people in the community.

The most concise way to remember this: HIV, positive chest x-ray, close contacts, severely immunocompromised **≥ 5 mm**; no risk factors **≥ 15 mm**; all the rest **≥ 10 mm**.

The **negative** TB skin test: Sometimes the result is a true negative; sometimes it's a false negative. Interpretation of the **negative** test requires that you consider the following:

- Was the test placed too soon? It takes up to **10 weeks** to react after an exposure. If a recently exposed patient has a negative TB skin test, recheck 10–12 weeks after exposure. Whether you treat this patient in the interim depends on whether you think the patient is really high-risk for TB (an individual judgment—not based on specific parameters). A nurse, for example, is more high-risk than an accountant.
- Can the patient actually react to the test? Is the patient possibly anergic? Worry about **anergy** in patients with immunosuppression (HIV/AIDS) and sarcoidosis. However, know that “control” tests are no longer recommended because, as we said, up to 25% of people with active disease have negative PPDs, even when their “control” test is reactive. Therefore, the control test does not help you interpret a nonreactive TB skin test—and in fact, has been a cause for misinterpreting test results in the past!

Here's the bottom line: If you **strongly suspect TB** in a patient (e.g., because they had an exposure and they are high-risk), then **start empirical treatment** even if the patient has a negative TB skin test result. And be aggressive about continuing the workup.

“New Converter” and the Booster Effect

The terms “new converter” and “booster effect” are used to discuss certain patients who are monitored with yearly skin tests; e.g., health care providers and nursing home patients.

The induration that occurs with TB skin testing is a delayed-type hypersensitivity reaction mediated by the memory T cell response to *M. tuberculosis*, non-tuberculous mycobacteria, or BCG.



Image 3-22: Properly reading the TB skin test (indurated area perpendicular to long axis of forearm)

Quick Quiz

- What is the percentage of patients who have active pulmonary TB and non-reactive TB skin tests?
- What do you do differently to read the TB skin test in the patient who has received the BCG vaccine?
- In what direction of the arm is the TB skin test read?
- In what groups of patients is a reactive TB skin test of 5 mm or more significant? 10 mm or more? 15 mm or more?
- List some reasons why a patient with true latent TB might have a negative TB skin test.
- What are you going to do for the patient who is high-risk for TB disease but has a negative skin test?
- What is the booster effect seen with TB skin testing?
- What is the definition of a “new converter”?
- Which patients should be screened with IGRA tests?
- Can a patient with a negative TB skin test still have TB? What about with a negative IGRA?

Now, some people's T cells “remember” better than other people's T cells. Most people who have LTBI will have induration within 48–72 hours of a skin test, but the sensitized people who have memory-impaired T cells will not respond within 72 hours (often, the elderly). Retesting a week later with a second TB skin test often stimulates the memory-impaired T cells to better recall previous antigen and indurate.

Stimulating T cells with bad memory in this manner is called “boosting.” The significant induration that occurs on the 2nd test, but was not visible on the 1st test, is called a “**booster effect**.” The booster effect can sometimes persist **several months** after the 1st TB test, so it becomes difficult to determine sometimes if new induration on a yearly screening skin test reflects the booster effect or new conversion from a recent exposure. (Then the patient is labeled a “**new converter**.”) A “new converter” has a **≥ 10 mm increase** in TB skin test **induration** within **2 years** from the 1st non-reactive test.

Here's the classic way that boosting gets confused with new conversion:

A nursing home patient or health care worker, who has constant potential exposure to TB, gets her 1st annual TB skin test. She has no reaction. One year later, during the required yearly TB screen, she now has 10 mm of induration. Is this new induration because she has developed

LTBI in the last year (and is thus a “new converter”), or is it due to boosting? **You don't know.**

Therefore, in patients who are scheduled for annual TB skin tests, a 2-step TB skin test regimen is often employed for the 1st screening. In the 2-step regimen, the patient gets an initial test, and if the initial test is nonreactive, then the patient is retested in a **week**, with the 2nd test establishing the patient's baseline result. If the patient has a negative baseline test but develops significant induration with the next year's test, you can say with certainty that the new induration is from recent exposure, and the patient is a “new converter.”

Know the definition of “new converter” and that TB skin tests are performed as a 2-step regimen for most patients who subsequently will be undergoing yearly TB screening.

Understand that 10 mm of induration in a nursing home patient or a health care worker is a “significant” result and merits **treatment** for LTBI **regardless** of whether it's a boosted result or a new conversion. The clinical difference is the patient's risk of reactivation TB within the next 2 years; risk is much **higher** after recent true **conversion** compared to a boosted result.

Interferon-γ Release Assays (IGRAs)

IGRAs are being actively used in clinical practice, and are endorsed by the CDC, to screen for active and latent TB **in lieu of** the TB skin test. Examples are the QuantiFERON®-TB Gold test and the T-SPOT®.TB assay.

These test for the γ-interferon released during TB infection. The tests cannot distinguish active from latent disease, and they should not be used to diagnose active TB because false negative tests in active disease can be a problem. The test is performed in a single day. There is no booster response. BCG does not cause a false positive result.

The current CDC recommendations for use of the test include:

- IGRAs are preferred over TB skin testing for non-adherent patients and for those who have been given BCG.
- TB skin testing is preferred in children < 5 years of age.
- All other patients can get either the IGRA or the TB skin test—but not both.

The IGRA should not be used in the health care worker with a positive TB skin test, as a way to escape being treated with isoniazid, if the IGRA is negative. These situations are complex, and neither the IGRA nor the TB skin test is perfect.

As with a negative TB skin test, a negative IGRA does not exclude infection in patients who have a high pretest probability of disease. Manage indeterminant tests based on likelihood of having TB.

Positive PPD Considerations

What do you do when a patient has a **positive skin test** or **IGRA**?

A positive test indicates that the patient has or has had LTBI, but not necessarily active disease. If the patient has had no previous TB workup, perform a workup for active disease: full review of systems and good physical exam, chest x-ray, sputum for acid-fast bacteria smear, culture, and at least 1 PCR test for *M. tuberculosis*. (Sputum testing is **not** required if the chest x-ray does not demonstrate abnormalities and the patient's review of systems is inconsistent with active disease.)

If the **PPD** or **IGRA** is **positive** and **active** disease is present, treat for active tuberculosis, as discussed next.

If the **PPD** or **IGRA** is **positive** and **no** active disease is present, treat for LTBI—regardless of age! This includes the 80-year-old and the 1-year-old, HIV-positive and HIV-negative, pregnant and not pregnant (although care must be given to minimize teratogenicity and hepatotoxicity during pregnancy).

Treatment for LTBI

Give isoniazid (INH) to eradicate the TB infection before it can develop into the disease. Again, the risk of conversion is 5% within 2 years for the general population and ~40% within several months for HIV patients (Table 3-13).

Treatment with **INH** for **9 months** is recommended for everyone except those with known exposure to

INH-resistant organisms or history of INH intolerance. Instead, in these cases, give **rifampin** for **4 months**. In the CDC's *Core Curriculum on TB* (2000), the recommendation was PZA + rifampin combination therapy—but this has proven **too toxic** and is no longer recommended. Do not use PZA in pregnancy because it causes birth defects.

Again, what about negative IGRAs or PPDs?

Patients who have been a **close contact** of someone with active TB but have a negative TB test can either be observed or treated for LTBI, depending on their risk; e.g., an HIV-positive patient would probably be treated, whereas a healthy person with no other risks would probably be observed. Children definitely get treatment. Retest the negative cases in 10–12 weeks.

Treatment of Active TB

The emergence of multidrug-resistant strains has changed the treatment of active tuberculosis. Let's first define the **4-drug** and **3-drug** regimens.

The **4-drug** regimen:

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)

and

- Either ethambutol (oral; preferred) or streptomycin (injection)

Table 3-13: Positive PPD Determination Based on Preexisting Conditions

Treatment of Latent Tuberculosis Infection

Certain groups are at high risk of developing TB disease once infected. These people are candidates for treatment regardless of their age—after ensuring active infection is not present. The current optimum treatment regimen for all patients is **9 months** of daily INH. See text for treatment of drug-resistant organisms. Treat **All** the following (**All ages!**):

PPD Result (induration)

In People with the Following Conditions

≥ 5 mm is positive in these high-risk groups

- Known/suspected HIV infection
- Close contacts of active cases
- Chest x-ray suggests previous inactive tuberculosis
- Organ transplants and other immunosuppressed pts with greater than 1 month of equivalent prednisone use (> 15 mg/d)

≥ 10 mm is positive in these intermediate-risk groups

- Recent immigrant from country with high prevalence
- Injection drug users
- Employees and residents of high-risk settings (prisons, jails, hospitals, nursing homes and other long-term care centers, homeless shelters, mycobacteriology lab workers)
- Patients with certain comorbidities (silicosis, diabetes, advanced chronic kidney disease, leukemia, lymphoma, solid tumor malignancies, recent weight loss of > 10% of ideal body weight, gastrectomy, post-jejunoileal bypass surgery)
- Children < 4 years of age and others with high-risk comorbidities

≥ 15 mm is positive in low-risk patients

- No known risk factors

PPD negative but high-risk

High-risk contacts of **active** cases

Quick Quiz

- What is the usual treatment (and for how long) for an asymptomatic, HIV-negative, 30-year-old with a positive TB skin test and normal chest x-ray?
- What is the usual treatment for latent TB? (Hint: The patient in last question has “latent TB.”)
- What are the 4 drugs used to treat active TB? How long is each given?
- What side effects are associated with the different anti-mycobacterial drugs? Required screening?
- What is Lady Windermere syndrome?

The **3-drug** regimen consists of the first 3 drugs (INH, RIF, and PZA; “**Rest In Peace**” for the TB patient who doesn’t get RIF, INH, and PZA). Remember: Do not use PZA in pregnancy.

In the U.S., all patients with active tuberculosis are initially to be treated for **2 months** with **4-drug therapy**, **unless** criteria for 3-drug therapy are met (see below). Give the first 3 drugs for the full 2 months, while the 4th drug may be dropped if the susceptibility testing shows sensitivity to the first 3 drugs. **After** the first 2 months, give **INH + RIF** for an additional **4 months**—i.e., 6 months total.

HIV-infected patients on protease inhibitors are usually given rifabutin instead of rifampin. Duration of therapy for HIV-infected patients is also 6 months but may be increased in patients with CNS or skeletal involvement or cavitary lung lesions that stay culture-positive.

Someone must **observe** all patients taking the medication unless compliance is absolutely assured. This “Directly Observed Therapy” (**DOT**) is supervised by the local health department.

When can **3 drugs** be used?

Only if there is a slight chance of drug-resistant infection. All the following criteria must be met:

- New TB patient and < 4% primary resistance to INH in the community
- No known exposure to a patient with a drug-resistant infection
- Is not from a high-prevalence country

Additional notes:

- Give vitamin B₆ (pyridoxine) with INH-containing regimens to prevent peripheral neuropathy and mild central nervous system effects.
- If the patient cannot take PZA, give INH and RIF for a total of 9 months.

- If the TB is resistant to INH only, stop INH and give the other 3 drugs for 6 months (total) or RIF and ethambutol for 12 months.
- Multidrug-resistant TB (i.e., to at least INH and RIF) is difficult to treat. Treatment is based on sensitivities.

Know these side effects:

INH, RIF, and PZA are **all hepatotoxic**.

INH: In **all** patients on INH, regardless of age, monitor monthly only for **signs and symptoms** of liver toxicity. Laboratory testing is indicated **only** if signs or symptoms develop!

Ethambutol is not hepatotoxic, but it can cause a decrease in **visual** acuity. Often, decreased color perception is the first sign of this deterioration. It is usually reversible if the drug is quickly discontinued. Patients should have an ophthalmologic exam before treatment and periodic checks thereafter (Snellen chart, gross confrontation eye exam, and question the patient). Any inflammatory disease of the eyes is at least a relative contraindication for ethambutol.

Streptomycin is an older aminoglycoside. It tends to cause ototoxicity and nephrotoxicity.

NON-TUBERCULOUS MYCOBACTERIA (NTM)

NTM include mycobacteria species other than *M. tuberculosis* and *M. leprae*. Many NTM species have been found to cause infections in humans, especially in immunoincompetent patients and in patients with bad lungs. Representative common examples include ***M. avium* complex** (MAC; includes *M. avium* and *M. intracellulare*), *M. kansasii*, and *M. goodii*. Importantly, these species are sometimes found incidentally in the sputum of healthy individuals.

Pulmonary Infections with NTM

Two basic groups of NTM clinical lung disease are seen:

Pattern 1: middle-aged male with underlying lung disease (e.g., COPD or bronchiectasis) who presents with cough, weight loss, and lung infiltration—possibly even cavities. This presentation is very similar to TB, but the progression is more indolent. Radiographs often are difficult to interpret owing to underlying lung disease.

Pattern 2: middle-aged female nonsmoker who presents with cough productive of purulent sputum and interstitial infiltrates on radiograph. When the infiltrates are in the right middle lobe or lingual, the presentation is termed **Lady Windermere syndrome**—based on a character from one of Oscar Wilde’s plays. Radiographs or CT scans often show bronchiectasis or nodules.

Because the humoral immune response of these two patient groups is generally intact, the NTM do **not** spread **outside** of the lungs.

Diagnosis is made using criteria by the ATS, which requires that a **HRCT** scan of the lungs show specific abnormalities (bronchiectasis and nodules) in addition to requirements for sputum results (2 or more samples culture positive for same organism or lung biopsy showing granulomas or +AFB with 1 culture positive). Nucleic acid probes are available to make a rapid diagnosis of MAC on sputum samples.

Employing the ATS criteria helps to avoid over-diagnosis of NTM lung disease and unnecessary treatment. Know that an isolated sputum sample growing NTM in a healthy person is not diagnostic of disease and does not require treatment!

Patients with severe immunodeficiencies (namely, AIDS with **CD4 counts** < 100/ μ L) are unable to hold the infection at bay in the lungs and, instead, develop disseminated disease with positive blood cultures and manifestations in the lungs, liver, and bone marrow. Patients present with constitutional symptoms and, often, diarrhea. Labs indicate systemic disease with leukopenia, anemia, and elevated transaminases—and blood cultures for mycobacteria are often positive.

Treatment of NTM is lengthy, tough, and should be guided by your culture results because not all bugs have the same susceptibility pattern. 2 antibiotics (clarithromycin and ethambutol) are given for isolated, non-cavitary, lung disease; and 3 antibiotics (clarithromycin, ethambutol, and rifampin) are used to treat cavitary lung disease and disseminated disease in AIDS.

Hospitalized patients with NTM do **not** require respiratory isolation (unlike patients with TB or suspected TB).

Cutaneous Infections

Know that NTM can cause infections of **surgical sites** in immunocompetent patients. Patients with immune deficiencies can have disseminated disease that starts with a skin infection. Some post-surgical patients have gotten infected plastic surgery sites after exposing their healing wounds to soil and water; e.g., a trip to the beach status-post tummy tuck. Think about these organisms if you see the classic history of recent plastic surgery, travel with exposure to sand and water, and indolent drainage from the surgical site: *M. abscessus*, *M. fortuitum*, *M. chelonae*, and *M. marinum*.

TB Skin Tests and NTM

Memory T cells that have been stimulated by NTM will react to the antigen in the TB skin test, but the reaction is usually not as robust as with true TB sensitization. Still, this reaction to NTM is why we have cut-off measurements for “significant” reactions with TB skin testing.

This is somewhat useful to know when you are evaluating a patient who has an indurated, but not significant, TB skin test result and AFB+ sputa (possibly the AFB

will end up being identified as NTM in culture). Nucleic acid amplification testing for *M. tuberculosis* is really helpful in this situation to exclude true TB.

IMMUNOSUPPRESSED PATIENTS

IMMUNE DYSFUNCTION

Note: The following is covered in more depth in the Infectious Disease section, Book 1, and in the Allergy & Immunology section, Book 4.

Bacterial pneumonia is the most frequent cause of death in immunodeficient patients. Mortality is 50%.

Humoral dysfunction: B-cell dysfunction or decreased antibodies are seen in most patients with ALL, CLL, and multiple myeloma. These patients are especially susceptible to **encapsulated** organisms, including *S. pneumoniae*, *H. influenzae*, and meningococci.

Patients with hypogammaglobulinemia, asplenia, sickle cell, or abnormal complement also have a tendency to acquire infections caused by the same encapsulated organisms.

Cell-mediated dysfunction: T-cell defects are seen in patients with AIDS, lymphoma, uremia, post-organ transplant, and after use of steroids or alkylating agents. These patients are susceptible to infections caused by encapsulated bacteria (pneumococcus); *Pneumocystis jiroveci* (PJP; previously *P. carinii*); mycobacteria; viruses, such as CMV and HSV; fungus (*Cryptococcus*); *Legionella*; and *Nocardia*. Although the incidence of PJP has dramatically decreased with use of prophylactic drugs and HAART, *Pneumocystis* remains the most common cause of pneumonia in AIDS patients (second is encapsulated bacteria such as *S. pneumoniae*). A minority of patients with ALL have T-cell variant, and these may have a T-cell deficiency.

Neutrophil dysfunction: AML, CML (the **myelogenous** leukemias), bone marrow transplant, and in others getting ablative chemotherapy. These patients tend to get infections with gram-negative organisms, staph species, *Corynebacterium jeikeium*, and fungi (*Candida* and *Aspergillus*).

ORGAN TRANSPLANT

Organ transplant patients get the same infections as patients with T-cell defects:

- During the **first 30 days**, patients most commonly get the usual nosocomial infections—especially **gram-negative** pneumonias and *Legionella*.
- **1–4 months**, *P. jiroveci*, CMV, and mycobacteria infections appear.
- **After 4 months**, think of *P. jiroveci*, encapsulated organisms, fungus (*Aspergillus* and *Candida*), and viral infections (include herpes). Also, community-acquired infections are common.

Quick Quiz

- What do you do for the healthy patient with a single sputum sample positive for *M. kansasii*?
- A patient returns from a vacation to Mexico with complaints of chronic drainage from a recent tummy tuck incision. What is a likely organism?
- What are the 2 most common causes of pneumonia in patients with HIV/AIDS?
- What is the preferred regimen for treatment of *Pneumocystis jiroveci*? How about with $P_aO_2 = 60$?

CMV infection is usually donor-to-recipient. The **majority** of renal and cardiac patients get CMV infections. It is the most common cause of **fever** after transplant! It usually occurs 6–8 weeks after transplant. CMV typically causes only a mild infection, but it is also responsible for 20% of deaths in cardiac transplants!

Think of CMV if there is a mixed bag of “-itises” because patients often get concurrent pneumonitis, hepatitis (usually mild), and adrenalitis-causing adrenal insufficiency!

Diagnosis: Finding inclusion bodies on BAL **suggests** CMV infection. Finding inclusion bodies on a tissue sample (lung biopsy) **confirms** the diagnosis.

Treatment: Ganciclovir, along with high-dose IV immunoglobulin infusion, has been beneficial in bone marrow transplant patients.

MYELOPROLIFERATIVE DISORDERS

If a patient with a myeloproliferative disorder gets a localized infiltrate, it is usually caused by a **gram-negative bacterial** pneumonia. Treat empirically.

LUNG PATHOGENS IN THE IMMUNOSUPPRESSED

Pneumocystis jiroveci and PJP

P. jiroveci and encapsulated bacteria (especially **pneumococcus**) are the most common causes of pneumonia in HIV/AIDS. *P. jiroveci* pneumonia (PJP) also remains the most common **opportunistic** infection in AIDS patients. A history of PJP and/or a **CD4 count of < 200** (or 14%) indicate greatest risk. The incidence of PJP in patients adherent to both antiretroviral therapy (ART) and PJP prophylaxis is near zero. Patients present with indolent, progressive dyspnea and cough with scanty sputum +/- fever. Think about PJP in any HIV+ patient with pulmonary symptoms. Chest x-ray usually shows diffuse, bilateral, symmetrical interstitial + alveolar infiltrates.

Diagnose with sputum examination using immunofluorescent monoclonal antibodies (reveals the organism in 80% of cases, while BAL or transbronchial biopsy gets the rest). Other ways to examine sputum are Giemsa stain and Gomori methenamine silver stain, but these tests are less sensitive than the monoclonal antibody.

Treatment: IV or oral TMP/SMX or IV pentamidine are preferred 1st line drugs. Try TMP/SMX first because it can eventually be given orally. Alternatives include atovaquone, dapsone/TMP, or clindamycin/primaquine, but these alternatives are for mild cases of PJP only. A majority of PJP patients improve on the initial course of therapy (usually 3 weeks), but a good number have intolerable side effects from treatment (e.g., rash and bone marrow suppression with TMP/SMX).

Corticosteroids given concomitantly with initiating anti-PJP treatment reduce the likelihood of respiratory failure and death in patients with moderate-to-severe pneumonia. Give **steroids** to PJP patients with a $P_aO_2 < 70$ or an A-a gradient > 35!

Bacterial Pneumonia

Bacterial pneumonia, usually due to *Streptococcus pneumoniae* or *Haemophilus influenzae*, occurs in HIV/AIDS patients with **CD4 counts ~ 300/ μ L**—higher than those with PJP. HIV-positive patients have 6x increased risk of pneumonia and **100x** increased risk of bacteremia with pneumococcus compared to HIV-negative individuals. Again: Pneumonia in a patient with risk factors for HIV, think PJP and pneumococcus.

Mycobacteria

Mycobacteria: For TB in HIV/AIDS, the treatment is the same as for any other patient (see previous section). Most AIDS patients with TB come from areas where there is already a **high** prevalence of TB.

The most effective treatment for NTM (*M. avium* complex; MAC) is to get the **CD4 count > 100** (with antiretroviral therapy) and initiate combination therapy against the MAC—usually using clarithromycin or azithromycin with rifabutin and ethambutol.

Fungi

Aspergillus

Aspergillus can cause invasive disease in patients with AML, ALL, Hodgkin disease, heart or bone marrow transplant, chronic corticosteroids, and with granulocytopenia lasting > 25 days (slow growing!). Occasionally, we see disease in AIDS patients.

Previously, we discussed *Aspergillus* in the asthmatic (see ABPA, [page 3-32](#)), but that's **not** what we're talking about here. In this section, we're looking at **invasive disease**. Sputum cultures growing *Aspergillus* are usually ignored in patients with competent immune systems because *Aspergillus* is often found incidentally in normal sputum.

The spectrum of *Aspergillus* disease depends on the immune system of the patient and includes aspergilloma, invasive sinusitis, **invasive pulmonary aspergillosis (IPA)**, and hematogenous dissemination to various organs (the most severe manifestation).

IPA is one of the **most feared** complications of treating heme malignancies because, prior to the last 5 years, mortality was very high.

Know that IPA presents as either an acute or an indolent pulmonary syndrome of fever, cough, dyspnea, and occasional hemoptysis in the severely immunocompromised patient. Occasionally, no symptoms are present in marrow transplant patients because they lack any immune response.

Diagnosis of IPA requires quick recognition of the clinical picture, HRCT of the chest (buzzword is “**halo sign**” = early evidence of pulmonary **infarction**), and lab tests. Lung samples can be obtained and cultured—sometimes the organism is visible in path specimens and grows in culture. **Galactomannan** is a polysaccharide that is a major component of *Aspergillus* cell walls. Because it is a water-soluble carbohydrate, it is found in blood, urine, CSF, and BAL of infected patients. This aids in the diagnosis of aspergillosis. Know that piperacillin-tazobactam (Zosyn®) contains a significant amount of galactomannan antigen and will give a **false-positive** test.

Aspergillomas are balls of fungus that grow in cavities from prior lung disease in immunocompetent people; e.g., TB, NTM, bullae. They present as very indolent disease of the lung with cough, hemoptysis, and constitutional symptoms. X-rays show cavities with fluid or fungus balls. Aside from chronic wasting and necrosis of remaining lung, the major complication is life-threatening **hemoptysis**. Sometimes patients do not develop typical fungus balls, but instead they have chronic infection of prior cavities with *Aspergillus*. This presentation is simply called “**chronic pulmonary aspergillosis**.” The galactomannan assay can also be used to diagnose chronic pulmonary aspergillosis, in addition to culture.

Treatment of *Aspergillus* infections depends on the form of disease:

- IPA in immunosuppressed: IV voriconazole (major reduction in mortality compared to amphotericin B)
- Aspergilloma (+/- hemoptysis): surgery
- Chronic pulmonary disease and ABPA: oral itraconazole + corticosteroids
- Sinus disease: surgery + antifungal (amphotericin B, azole, or echinocandin)

Cryptococcus

Cryptococcal pulmonary disease is associated with Hodgkin disease, corticosteroids, and transplants but **not** with PMN defects or neutropenia. Chest x-ray may show nodules or mass lesions. *C. neoformans* in sputum **equals** infection (contrary to *Aspergillus*). Needle aspiration and lung biopsy are also accurate means of

diagnosing cryptococcal pneumonia. If found, perform a lumbar puncture to evaluate for CNS infection. Patients with HIV/AIDS and **CD4 counts < 100/μL** are susceptible to meningitis.

Coccidioides

Coccidioides immitis is endemic in the southwestern U.S. (California and Arizona). Most immunocompetent patients with infection are asymptomatic or develop a **mild** influenza-like illness that is self-limited. Disseminated or chronic infections are most common in patients with myeloproliferative disorders, Hodgkin disease, transplants, and AIDS.

Histoplasma

Disseminated histoplasmosis is common in AIDS patients with CD4 counts < 100/μL who live in endemic areas, such as the southern and midwestern U.S. It is especially found in the Mississippi and Ohio River valleys.

Nocardia

Nocardia asteroides lung infections are usually seen in T-cell deficient patients (not those with humoral deficiency) and in patients with pulmonary alveolar proteinosis. The pulmonary lesions may cavitate. Brain abscesses and subcutaneous dissemination may occur. Treat with sulfonamides.

Candida

Candida pneumonia is **very difficult** to diagnose in immunosuppressed patients. *Candida* in the sputum is nonspecific. Very rare occurrence.

Zygomycosis

Pulmonary zygomycosis (previously mucormycosis)—patients with **leukemia** are at especially high risk. It is also seen in uncontrolled **diabetics** with frequent DKA. This infection has a **poor** prognosis.

Reactivation Infections

Besides TB, toxoplasmosis, herpes infections, cryptococcosis, and strongyloidiasis can reactivate in the immunosuppressed.

NONINFECTIOUS INFILTRATES

Drugs may have cytotoxic or non-cytotoxic lung effects:

- Methotrexate is the most common cause of **non-cytotoxic** lung reactions and causes a hypersensitivity interstitial pneumonitis.
- Bleomycin is the most common cause of cytotoxic pulmonary toxicity.

Quick Quiz

- Discuss the various types of *Aspergillus* pulmonary infections.
- What is the recommended treatment of invasive pulmonary aspergillosis?
- Name some causes of noninfectious pulmonary infiltrates.
- Gold-induced lung disease is reversible—just stop the drug.
- Bleomycin, amiodarone, and the nitrosoureas all cause **dose-related** pulmonary disease, while almost all other offending drugs have a hypersensitivity or idiosyncratic effect. Uremia, supplemental O₂, and radiation therapy exacerbate bleomycin lung toxicity. Transbronchial lung biopsy is the diagnostic procedure of choice, but it is usually not needed.
- **Crack** cocaine can cause a hypersensitivity pneumonitis, diffuse alveolar hemorrhage, and COP.

Hemorrhage is **common** in patients with **AML**—it can be the **sole** cause of pulmonary infiltrates in these patients. But remember: In AML, rule out *Aspergillus* infection as the cause of the hemorrhage. (Also remember, hemorrhage may be caused by idiopathic pulmonary hemosiderosis, Goodpasture's, SLE, and post-bone marrow transplantation.)

Leukemic pulmonary infiltrates most commonly occur in **ALL**, and they **always** imply a high percentage of blasts. Leukostatic infiltrates (globes of WBCs in the pulmonary **vessels**) occur in myeloid leukemias when the WBC count is > 100,000. Half of **lymphoma** patients have infiltrates.

Radiation changes in the lung usually present **within 6 months** of treatment. These changes are divided into 5 phases with radiation pneumonitis (the acute inflammatory reaction) occurring within 6 weeks. Radiation changes (pneumonitis/fibrosis) have a characteristic chest CT appearance with **sharp boundaries** corresponding to field of radiation exposure.

CRITICAL CARE

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Overview

Acute lung injury is defined as:

- Ratio of $P_aO_2/F_iO_2 \leq 300$, regardless of amount of PEEP
- Bilateral pulmonary infiltrates
- PCWP ≤ 18 mmHg (or no clinical evidence of left heart failure)

ARDS is defined as an acute lung injury in which the $P_aO_2/F_iO_2 \leq 200$. ARDS can have a **direct or indirect** precipitating event. **Direct** causes include aspiration, pneumonia, and inhalation injuries. **Indirect** events are sepsis, pancreatitis, multiple transfusions, and trauma. Aspiration and sepsis are the most common. With multiple precipitating events, risks increase.

A mnemonic:

- A (acute onset)
- R (restrictive lung mechanics)
- D (diffuse panendothelial inflammatory injury manifested in the lungs)
- S (shunt hypoxemia)

There is a **48–72-hour** lag time between injury and ARDS. As yet, it is unknown what all of the factors are that cause the leaky lungs in ARDS. Injury results in local edema with subsequent fluid accumulation in the interstitium and alveoli, compounded by the presence of inflammatory cells and their mediators. The inflammation causes all sorts of chaos in the lungs: microthrombi clot local vessels; protein aggregates, surfactant, and cellular debris that clog up the alveoli in “whorls.” Inflammatory cells invade the interstitium and alveoli en masse, releasing more mediators and causing a ruckus. Eventually large sections of lung simply collapse, which causes shunting and hypoxemia. The microthrombotic occlusion of pulmonary vessels leads to nonperfusion of ventilated areas, causing dead space and hypercapnia—in addition to the hypoxemia (**Image 3-23** and **Image 3-24**).

Patients initially present with symptoms of the underlying cause plus dyspnea, increased work of breathing, and eventual respiratory fatigue.

With supportive care, patients improve and enter a “proliferative phase,” where their lungs repair and organize. Usually this is when they can be weaned from ventilator support. A few patients will go on to develop fibrosis as part of healing and will remain ventilator and/or oxygen dependent for a prolonged period. As yet, there is no prophylaxis for ARDS.

Death rate is 25–58% and has not decreased significantly since 1994, when the current definition of ARDS was determined. Death due to respiratory failure in ARDS is **uncommon**! The most common cause of death within the first 3 days after onset of ARDS is the underlying problem. After 3 days, nosocomial **pneumonia** and **sepsis** are the most common causes of death.

Making the diagnosis of pneumonia in the patient with ARDS is difficult because infiltrates and leukocytosis are common in ARDS. Lavage fluid in ARDS without pneumonia has nearly 80% PMNs (normal < 5%). Quantitative airway cultures (as discussed in the section on HCAP) are a valid approach to diagnosing pneumonia in these patients. Give antibiotic therapy as indicated by Gram stain and C+S results.

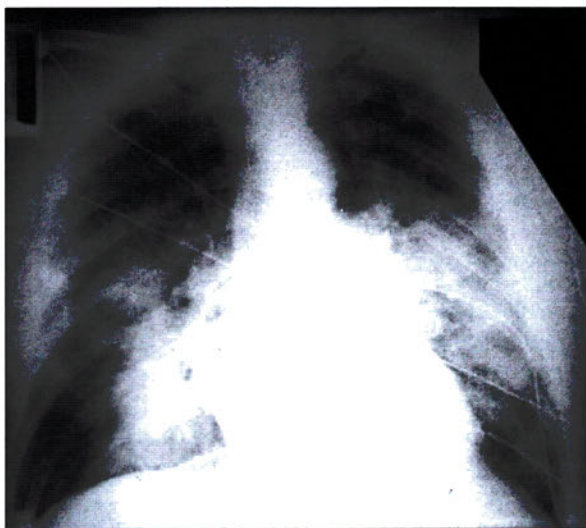


Image 3-23: AP Chest showing ARDS

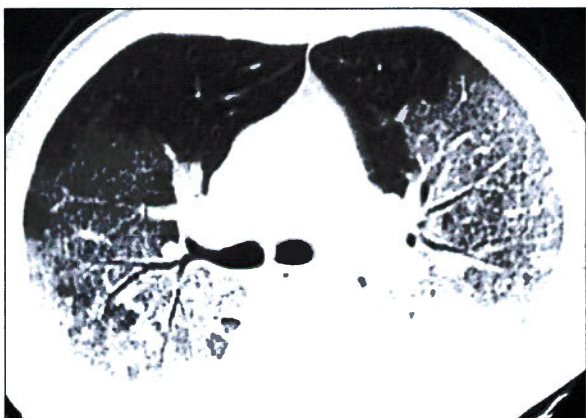


Image 3-24: CT Chest showing ARDS

Prevention of pneumonia in the ARDS patient is important. Adequate handwashing and using sterile technique are mandatory. Selective decontamination involves using antiseptic solutions or topical antibiotics to reduce colonization in the upper airway and GI tract. It does decrease the risk of VAP, but it does not improve mortality and is expensive and time consuming.

Treatment

Overview

Treatment of ARDS: **Treat the causative condition** and provide optimized **cardiopulmonary support**. If the patient has an abscess, push surgeons to remove it or interventional radiology to drain it. Give empiric antibiotics if sepsis is thought to be the cause.

Keep patients slightly hypovolemic, **but** it is very important to provide enough volume to maintain adequate cardiac output and tissue-oxygen delivery—thereby preventing worsening lactic acidosis (and the resultant multiorgan failure).

ARDS Network FACT trial demonstrated that conservative fluid replacement (targeting normal central venous

pressure [CVP]—pulmonary artery occlusion pressure [PAOP]—hemodynamic function) was better than a liberal strategy. It led to decreased ICU and ventilator time and decreased organ dysfunction. Mortality, however, was similar. This trial also concluded management with CVP is as good as using a PA catheter. This fluid algorithm is on www.ardsnet.org.

Nutrition should be **enteral** rather than parenteral, if possible. There is not only less chance of catheter-induced sepsis, but enteral nutrition possibly prevents translocation of endotoxin and gram-negative colonic bacteria. Recent studies with special formulae high in omega-3 fatty acids have shown benefit in ARDS and septic shock.

Ventilator Support for ARDS

PEEP stands for positive end-expiratory pressure; on the ventilator, a valve shuts when the patient is near end-expiration, while there is still positive intrathoracic pressure.

The trouble with ARDS is that it has shunt physiology, and the only way to improve oxygenation is to recruit, or “pop open,” some of the fluid-filled alveoli. At the same time, you want to avoid barotrauma and oxygen toxicity. To avoid oxygen toxicity, get $F_iO_2 < 60\%$ ASAP. To “pop open” alveolar units, use PEEP; but to avoid ventilator-induced lung injury (VILI), use **adequate, but not excessive**, PEEP.

Ventilator management **has now changed** with the recognition of the potential for ventilator-induced lung injury (VILI), which arises from overdistended alveoli (from an $\uparrow V_T$ or $\uparrow$ end-inspiratory plateau press) **and** cyclic opening and closing of atelectatic alveoli (recruitment-derecruitment). An adequate level of PEEP prevents repetitive closure and opening of lung units. Recommendations from the NIH ARDS Network indicate improved outcome with low tidal volumes (V_T) = 6 mL/kg and PEEP at adequate levels (discussed below). It turns out that maintaining low V_T appears to be critically important, and, for now, **6 mL/kg** is considered the optimal V_T . Generally, we start worrying about VILI due to excessive plateau pressures at > 30 cm H_2O .

Previously, V_T in the range of 12–15 mL/kg had been used, but this is **too high** for many patients with ARDS because their total lung capacity is much smaller than normal. There is a trend to lower tidal volumes in **all** patients on ventilators, whatever the cause.

No single ventilator mode has proven better than another for ARDS patients. An assist-control, volume-cycled ventilator mode was used in the ARDS Network trial.

Initial settings:

- $F_iO_2 = 1$ (then follow P_aO_2 goal as per [Figure 3-8](#)).
- V_T = start at 8 mL/kg ideal body weight and work down (6 is optimal). Monitor end-inspiratory plateau pressure! Maintain < 30 cm H_2O .
- Inspiratory flow = 60 L/min.

Quick Quiz

- Characterize the ARDS Network approach to fluid management in patients with ARDS.
- For ARDS, what is considered the optimal ventilator setting for tidal volume?
- Describe the ventilator-induced lung injury (VILI) that can happen when treating ARDS.
- Describe the specifics of permissive hypercapnia.
- PEEP: See the NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary in [Figure 3-8](#).
- Some physicians use a PEEP pressure just greater than the lower inflection point on the ventilator P_V curve. And yet others use an empiric regimen, in which they adjust the PEEP to maintain adequate S_aO_2 of at least 90% and low enough F_iO_2 (< 60%). PEEP usually starts at ≤ 5 cm H₂O and usually goes up to 10–20 cm H₂O. More on PEEP on [page 3-70](#).
- Surfactant replacement, inhaled nitric oxide (investigational), and recruitment maneuvers (e.g., patient positioning) are often added to help improve oxygenation.
- A bit on patient positioning: Usually, the lateral decubitus position is tried first. The prone position is problematic on a ventilator (!) but also may help.
 - Data support increasing the P_aO_2/F_iO_2 ratio with prone positioning, which stabilizes the anterior chest wall, causing improved physiology and recruitment of previously unused alveolar units.
 - The prone position was found to get the heart off of the left lower lobe and help with expansion.
 - The prone position is associated with pressure necrosis complications of the face and anterior body surface. In fact, all kinds of bad things can happen to intubated patients who are face down, if the ICU team is not experienced with prone positioning; e.g., extubation, venous catheters fall out, even fractures.
 - Recent data confirm no survival benefit from “proning.”

The above interventions aim to increase oxygenation. Know that none of them have been shown to improve survival, even though they improve P_aO_2 .

Permissive hypercapnia: The “ARDS Network low TV protocol” is based on studies of (and is meant for) patients with acute lung injury (ALI) or ARDS. These study results showed a mortality decrease. Specifically, some evidence suggests that respiratory acidosis may decrease lung injury and be protective. Permissive

hypercapnia is now the recommended ventilatory support for all patients with ARDS.

The **technique** of permissive hypercapnia:

Low V_T with a low V_E (minute ventilation) results in an **elevated P_aCO_2** (permissive hypercapnia). The goal is to not worry about the P_aCO_2 so much as maintain adequate tissue oxygenation in an ARDS patient—maintain the $S_aO_2 > 88\%$.

Hypercapnia is allowed to develop. The resultant acidosis can be corrected by any of the following:

- Increasing respiratory rate (RR)
- Increasing V_T if end-inspiratory plateau pressure is low
- Use $NaHCO_3$

Remember: Giving $NaHCO_3$ typically results in a subsequent increase in CO_2 as $NaHCO_3 + H^+ \leftrightarrow Na^+(Cl^-) + H_2O + CO_2$.

Renal compensation for the respiratory acidosis usually ensues, and typically you do not need to give an alkali or increase the V_E . Permissive hypercapnia is used in severe exacerbations of obstructive lung disease as well. Again, the therapy-determining measurement is S_aO_2 , not P_aCO_2 .

Permissive hypercapnia is not used with intracranial hypertension or hemodynamic instability.

Trials show **no** proven survival advantage in the following treatments for ARDS: high-frequency ventilation, extracorporeal respiratory support, surfactant administration, NSAIDs, antientotoxin therapy, and n-acetylcysteine (as an antioxidant).

To summarize, when using the ventilator in the treatment of ARDS, avoid VILI and oxygen toxicity by doing the following:

- Start V_T at 8 mL/kg and reduce to 6 mL/kg when able.
- Start F_iO_2 at 1 and follow the recommendations by the ARDS Clinical Network ([Figure 3-8](#)).
- Use adequate but not excessive PEEP.
- Use permissive hypercapnia if needed.
- Follow the mentioned ARDS Network PEEP dosing tables (on [ardsnet.org](#) and reproduced in [Figure 3-8](#)).

Medications for ARDS

There is no standard of care yet for the use of any medication, so the Boards should not cover this topic.

That being said, glucocorticoids have been the focus of several studies. Evidence ebbs and flows in favor of steroids. Currently, the standard of care is **not** to use them, although the ARDS Network currently is evaluating their use in late-phase disease.

**NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary**

INCLUSION CRITERIA: Acute onset of

1. $P_aO_2/F_iO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW; kg)
Males = $50 + 2.3 [\text{height (inches)} - 60]$
Females = $45.5 + 2.3 [\text{height (inches)} - 60]$
2. Select Assist Control Mode
3. Set initial TV to 8 mL/kg PBW
4. Reduce TV by 1 mL/kg at intervals ≤ 2 hours until TV = 6 mL/kg PBW.
5. Set initial rate to approximate baseline VE (not > 35 bpm).
6. Adjust TV and RR to achieve pH and plateau pressure goals below.
7. Set inspiratory flow rate above patient demand (usually > 80 L/min)

OXYGENATION GOAL: P_aO_2 55–80 mmHg or SpO_2 88–95%

Use incremental F_iO_2 /PEEP combinations below to achieve goal. Higher PEEP options (lower row) will decrease F_iO_2 and may be preferred in patients with high F_iO_2 who can tolerate higher PEEP (stable blood pressure, no barotrauma). Survival is similar with both PEEP approaches.

F_iO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
	12–14	14	16	16	18–20	20	20	20

F_iO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24
	20	20–22	22	22	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H_2O

Check Pplat (0.5 second inspiratory pause), SpO_2 , Total RR, TV and pH (if available) at least q 4h and after each change in PEEP or TV.

If Pplat > 30 cm H_2O : decrease TV by 1 mL/kg steps (minimum = 4 mL/kg).

If Pplat < 25 cm H_2O : TV < 6 mL/kg, increase TV by 1 mL/kg until Pplat > 25 cm H_2O or TV = 6 mL/kg.

If Pplat < 30 and breath stacking occurs: may increase TV in 1 mL/kg increments (maximum = 8 mL/kg).

pH GOAL: 7.30–7.45**Acidosis Management: (pH < 7.30)**

If pH 7.15–7.30: Increase RR until pH > 7.30 or $P_aCO_2 < 25$ (Maximum RR = 35).

If RR = 35 and $P_aCO_2 < 25$, may give $NaHCO_3$.

If pH < 7.15 : Increase RR to 35.

If pH remains < 7.15 and $NaHCO_3$ considered or infused, TV may be increased in 1 mL/kg steps until pH > 0.15 (Pplat target may be exceeded).

Alkalosis Management: (pH > 7.45) Decrease vent rate if possible.

**Figure 3-8: NIH NHLBI ARDS Clinical Network
Mechanical Ventilation Protocol Summary**

SEPSIS

Critically ill patients (especially sepsis $\pm$ ARDS) can have a **normal** P_aO_2 and still have **abnormal** O_2 uptake by the tissues. This is thought to be a major contributor to multiple organ failure.

Hypophosphatemia **decreases** diaphragmatic contractility in addition to shifting the O_2 saturation curve to the left. **Sucralfate** can cause this!

Careful! **Mixed venous** O_2 may be **misleading** in the septic patient because there is significant peripheral shunting. Lactic acid levels may be misleading as an indicator of tissue hypoxia because an increase can also be caused by failure of the liver to clear it. However, the measurement of these data is pivotal as stated in the Surviving Sepsis Campaign.

Always correct the underlying problem. You may do surgery/drainage on a focal infection if that is causing the sepsis, **even if** the patient is **unstable**.

The utility of pulmonary artery catheterization is controversial in most cases of sepsis. Remember the following general principles regarding PCWP:

- Pulmonary capillary wedge pressure (PCWP) reflects LVEDP, and LVEDP is an indicator of LV health; it reflects compliance and stroke volume.
- Always read the PCWP at end-exhalation.
- Read wedge pressure in all patients on a graphed wave form (not digital printout).
- Never take patient off PEEP to read the PCWP.

LVEDP is now **more often** determined **directly** during **left** heart catheterization just before contrast ventriculography (rather than during a right heart cath). More on PCWP in the Cardiology section, Book 3.

MECHANICAL VENTILATION**Overview**

The cuff of the tracheal tube should be inflated to the lowest possible pressure, ~ 15 mmHg. When the pressure exceeds ~ 25 mmHg, serious damage can occur to the tracheal mucosa.

Do a tracheostomy **only** after 2–3 **weeks** of intubation (barring other indications). Tracheostomy is not indicated to decrease airway resistance during weaning.

Ventilator-associated pneumonia is a frequent complication of mechanical ventilation. We discussed this in the section under VAP (page 3-54). Quick review: all patients are colonized with gram-negative bacteria in upper and lower airways within 74–96 hours. It may be very difficult to sort out true pneumonia vs. colonization. For a diagnosis of pneumonia, you should see:

- New or increasing infiltrate
- Leukocytosis
- Purulent sputum or endotracheal secretions
- Fever or hypothermia

Quick Quiz

- Discuss the different modes of mechanical ventilation.
- Name the “DESAT” causes of failure to wean.

Even with this clinical scenario, there is an ongoing debate about whether more invasive tests should be done to confirm the diagnosis. More invasive tests include PSB/BAL with quantitative cultures. Empiric antibiotic treatment for VAP should cover both *Pseudomonas* and MRSA.

Modes of Mechanical Ventilation

Continuous Ventilation

Controlled mechanical ventilation (CMV) has a set rate and set tidal volume that does not allow spontaneous breathing. Patient-ventilator asynchrony is a big problem; therefore, this mode is best used for those patients who are under anesthesia, paralyzed with muscle relaxants, or in deep coma.

Assist/Control (AC): This is a CMV with a set rate and tidal volume, but this mode allows the patient to initiate additional breaths. When the machine senses that the patient is attempting to take a breath, it will kick in with a full “machine breath” at the tidal volume you selected. This is a very commonly used mode of ventilation. One caveat: If patients are anxious and hyperventilating, they will continue to trigger additional full machine breaths, will get even more hyperventilation, and will be at risk for developing auto-PEEP.

Intermittent Ventilation

Synchronized intermittent mandatory ventilation (SIMV) is similar to AC in that you dial in a set rate and tidal volume, but **spontaneous breath overrides** the machine. Because this spontaneous breath requires a lot of work from your patient to suck in a breath through the endotracheal (ET) tube and the ventilator circuit, we often add **pressure support ventilation** (PSV) to the SIMV mode so that, when the patient takes a spontaneous breath, there is a boost of pressure (you set the amount) to help overcome the resistance of the ET tube and the ventilator circuit. Typically, use pressure support of 8–20 cm H₂O, **but** you need to titrate this pressure for an individual patient after you see what kind of spontaneous tidal volume the patient can generate.

Note: The above volume-cycled ventilators have a “pop-off” valve set at a certain inflation pressure to prevent over-pressurization of the lungs.

Pressure support ventilation (PSV), as discussed previously: In a spontaneously breathing patient, you can supply only pressure support, and there is no need for

mandatory breaths. This is a very comfortable mode for the patient in that he determines his respiratory rate and tidal volume. **However**, you **must** have a patient with a stable respiratory drive (i.e., not sedated heavily), and, most importantly, remember: There is **no guarantee what tidal volume** will be generated at a specific level of pressure support (no consistent direct correlation between tidal volume and pressure). If your patient is prone to—and develops—acute CHF, the lungs may acutely become “stiffer,” and the unchanged level of pressure support will produce a much smaller tidal volume, causing tachypnea and respiratory distress.

Pressure Control: a newer form of ventilation that is actually a throwback to the first ventilators. Machine breaths are pressure-cycled, not volume-cycled. You determine the pressure you want the patient to receive on each breath and the rate at which the breaths will be delivered. If the patient attempts a spontaneous breath, he will get a machine breath at the pressure you have designated. This may be helpful in limiting airway pressures in patients with high end-inspiratory plateau pressure in other volume-cycled modes that leave them susceptible to barotrauma. As with PSV, there is **no guarantee to the tidal volume**; hence, this mode must be titrated carefully at the bedside to determine the proper pressure settings.

Weaning and Failure to Wean

Weaning is now felt to be best accomplished using protocols. Generally, you do it in one of the following ways:

- Spontaneous breathing with a T-tube (SBT) protocols generally recommend progressively longer periods of breathing on a T-tube—from 10 minutes to 2 hours. Usually, once the patient tolerates 2 hours on the T-tube, the ET tube is removed. SBT can also be accomplished on the ventilator (to allow tracking of RR, V_T, and V_E), using low level of PS (PS + 5 cm H₂O) or tube compensation.
- PSV, wherein the pressure is gradually reduced to the point where it is just overcoming the resistance of the ET tube. This is, in practice, pretty difficult to determine because resistance of the ET tube can vary from 3–14 cm H₂O (!) due to differing diameters and lengths, kinks, and deformations.

Failure to wean—possible causes (**DESAT**):

- **Drugs** (e.g., sedatives).
- **Endotracheal tube** and **Electrolyte imbalance**. Sometimes the tube has too small of an intraluminal diameter. Besides a full-sized ET tube inducing resistance, it is common for ET tubes to decrease in diameter with time after placement. Automatic tube compensation is a newer ventilatory mode that dynamically compensates for the increased resistance of the ET tube, thereby making the final stages of weaning more predictable. Low levels of calcium, phosphorus, and magnesium impair weaning.

- Secretions.
- Alkalemia (decreases respiratory drive).
- Too high a P_aO_2 and too low a pCO_2 just before extubating (should keep it near the patient's baseline).

There is potential danger in stopping positive pressure ventilation. Stopping $\rightarrow$ increased venous return $\rightarrow$ increased blood flow $\rightarrow$ increased cardiac output $\rightarrow$ CHF/cardiac ischemia in susceptible patients. COPD patients with respiratory failure are less able to get rid of CO_2 ; and CO_2 production is increased with fever and with large amounts of glucose and other carbohydrates in the diet. Severe COPD patients, then, may be harder to wean if they have a fever or have had a high-carbohydrate diet.

Adjusting a Ventilator

Remember: When we are adjusting a ventilator to improve a patient's ABGs, we have to separate our actions into 2 categories:

- 1) Those that change alveolar ventilation (V_T and rate) = will change the patient's pCO_2 and pH. Remember alveolar ventilation is inversely proportional to P_aCO_2 . Alveolar ventilation = $(V_T - V_P) \times RR$ (where V_T = tidal volume and V_P = dead space).
- 2) Those that alter a patient's oxygenation = F_iO_2 , PEEP, Inspiratory/Expiratory Ratio.

PEEP

Positive end-expiratory pressure (PEEP) is a positive pressure left in the chest at the end of exhalation. This can be done purposely to a patient on a ventilator by closing a valve during exhalation and not allowing the pressure in the airways to return to zero.

You dial in a PEEP pressure—the desired end-expiratory pressure—typically 5–15 cm H_2O (can go higher in ARDS). The purpose of utilizing PEEP in mechanically ventilated patients is to help prevent the alveoli from completely collapsing at end-expiration. This prevents atelectasis and, more importantly, leads to better matching of V/Q while having less shunt fraction. PEEP also prevents atelectrauma, which is damage caused by shear forces that arise during repeated reexpansion of collapsed lung units.

Use PEEP only with diffuse lung disease! It can actually decrease the P_aO_2 if used in focal lung disease. Use PEEP in cases of diffuse lung disease if required to maintain the $F_iO_2 < 50\%$, while keeping the $P_aO_2 > 60$.

PEEP too high can cause:

- Pneumothorax, ventricular failure, and/or alveolar damage, which can precipitate or worsen pulmonary edema. The PEEP level recommended is just past the lower inflection point on the pressure-volume curve.
- Decreased venous return, causing decreased cardiac output and hypotension.

Auto-PEEP

Auto-PEEP usually happens when the time constant of the lung is violated in patients with high compliance and/or high airway resistance (high respiratory rate, high TV, high bronchospasm).

In essence, the patients are not fully emptying their lungs during expiration prior to the initiation of the next breath. This is known as “stacking breaths” or generating auto-PEEP. A patient on a ventilator gets auto-PEEP if the ventilator is set up in a way so as not to allow the patient to fully exhale before initiating the next breath. This is particularly worrisome in patients who have exacerbations of COPD or status asthmaticus requiring mechanical ventilation. In ventilated patients, the auto-PEEP may become severe enough that the patient may suffer barotrauma or hemodynamic collapse due to the inability of blood to return to the chest.

Auto-PEEP can be measured in mechanically ventilated patients using either of 2 methods:

- 1) Insert an end-expiratory pause in the ventilator circuit and observe the airway pressure monitor during the pause.
- 2) Use newer generation ventilators that automatically measure this for you at the touch of a button.

Treatment of auto-PEEP includes one or more of the following:

- Decrease respiratory rate.
- Decrease V_T .
- Increase TE (expiratory time).
- Increase PIFR (peak inspiratory flow rate).
- Decrease secretions.

What do you do if your patient with severe airway obstruction has hypotension after being placed on mechanical ventilation?

- 1) Disconnect the patient from the ventilator and slowly bag the patient through the endotracheal tube. Check for tension pneumothorax, mucus plugs, and that the ventilator is functioning properly.
- 2) Return the patient to the ventilator with new settings that allow for a longer expiratory phase. Specific changes: Lower the respiratory rate, increase the peak flow (shortening the time the patient gets for inspiration and, hence, allowing longer time for expiration), and reduce the tidal volume being delivered.

Note that the patient must be sedated or sedated + paralyzed to adequately measure auto-PEEP.

As an historical reference, inverse ratio ventilation is a technique that has been employed in patients with ARDS, whereby auto-PEEP was purposely generated as a mechanism for “recruiting” alveoli. It's fallen out

Quick Quiz

- What are the 2 categories of actions you keep in mind when adjusting a ventilator?
- When should you use PEEP?
- A patient with severe COPD is placed on the ventilator. She suddenly becomes hypotensive. What steps should you follow to stabilize her?
- What is the best route to provide nutrition for a mechanically ventilated patient?
- What is the refeeding syndrome, and how do you prevent it?

of favor since the lung protective strategy was published by the ARDS Network and because of the significant potential for harm and rare utility.

NUTRITIONAL SUPPORT

Nutritional support is **extremely important** and often not given enough emphasis. Use the **enteral** route whenever possible. After major surgery or the onset of sepsis, metabolic requirements increase dramatically. Requirements peak in 3–5 days. If the patient is unable to eat, start enteral feedings or TPN **as soon as possible after the initial insult**. Even though enteral feeding increases the possibility of aspiration, it is preferred over TPN because it tends to maintain the intestinal epithelium and its natural defenses against bacteria.

Enteral feeding is contraindicated in only 2 cases:

- 1) Patients with severe pancreatitis and associated abdominal pain
- 2) Prior to, and just after, abdominal surgery (Even in this situation, surgeons will feed immediately post-op when using a jejunostomy.)

Otherwise, feed enterally! With enteral feeding, you can decrease the risk of aspiration and pneumonia by keeping the head of the bed elevated > 30°. Position of head is more important than where the feeding tube is placed; e.g., pre- vs. post-pyloric.

Refeeding syndrome occurs when severely malnourished patients are fed high-carbohydrate loads. These patients develop low total body levels of phosphorus, magnesium, and potassium. With refeeding syndrome:

- There is a dramatic increase in circulating insulin levels and a resulting swift uptake of **glucose, K⁺, phosphate, and magnesium** into the cells—with a precipitous drop of these agents in the serum. The resulting severe hypophosphatemia causes heart and respiratory failure; rhabdomyolysis; RBC and WBC dysfunction; seizures; and coma.
- The body also begins to retain fluid (unknown why), and heart failure may result.

Prevent refeeding syndrome by starting the feeding of severely malnourished patients slowly, and aggressively give **phosphate, potassium, and magnesium** supplementation.

PULMONARY ARTERY CATHETERIZATION

Overview

Right heart and pulmonary artery catheterization is done with a balloon-floated (Swan-Ganz) catheter.

- As the catheter is introduced—usually via the internal jugular vein—take pressure readings of the central venous pressure, right atrial (0–8 mmHg = normal), right ventricle (0–8 end-diastolic; 15–30 systolic), and pulmonary artery (3–12 end-diastolic; 15–30 systolic) pressures.
- When the catheter has been flow-directed to a small pulmonary artery, the balloon at the tip can be temporarily fully inflated, and the reading (wedge pressure) is the dampened left atrial pressure (LAP—normals are: A wave: 3–15; V wave: 3–12; mean: 5–12 mmHg). LAP is a reflection of LVEDP in a patient with a normal mitral valve. LVEDP is a reflection of LV preload (assuming compliance is not changed). This LVEDP is the all-important indicator of the likelihood for LVF and pulmonary edema.

Thermal-dilution cardiac output (CO) is done by injecting a **known temperature** (usually ice water at 32° F but may be room temperature) and **known volume** of water 30 cm proximal to the tip of the PA catheter, then measuring temperature at the tip of the catheter. These values are put into a formula that calculates CO, taking into account temperature at the tip and the volume and temperature of the fluid (D5W) injected.

The greater the difference in temperature, the higher the CO—because more warm blood is mixed with the fluid injected from the proximal catheter port before it reaches the distal tip.

Mixed venous oxygen saturation (S_{vO_2}). This is the last measurement of venous blood before it gets oxygenated. Normally, the S_{vO_2} is 78%. This number drops as the global tissue oxygen debt increases. If it gets too low, you must boost delivery of O_2 to the tissues (increase O_2 sat, cardiac output, or Hgb concentration—discussed at the beginning of this section).

Systemic vascular resistance (SVR) measurement reflects vascular tone: vasodilated vs. vasoconstricted.

$$SVR = (MAP - CVP) \times 80/CO$$

(MAP = mean art press; CVP = central venous press)

Complications of PA Catheterization

Establishing central venous access can cause unintentional puncture of nearby arteries, bleeding, neuropathy, air embolism, and pneumothorax.

Advancing the catheter may cause dysrhythmias, which are usually transitory but may be persistent. Cardiac advancement can cause right bundle-branch block; and, in a patient with left bundle-branch block, this may result in complete heart block.

Catheter residing in the pulmonary artery may cause pulmonary artery rupture (53% mortality), venous thrombosis, thrombophlebitis, pulmonary embolism, and pulmonary infarction.

The majority of ICU physicians believe PA catheterization is helpful in select groups of critically ill patients. Even so, despite over 30 years of use, there is little proof that Swan-Ganz catheters have improved patient outcomes. Indeed, in a review of PA catheterization (Conners, et al. *JAMA* 1996) evaluating outcomes (survival, ICU and total length of stay, costs) in patients at 5 teaching hospitals, **each of the outcomes was worse for the patients undergoing PA catheterization!** One explanation has been that perhaps the hemodynamic information supplied by the PA catheter was not acted on optimally. You should weigh the risks and benefits carefully for each patient.

FACT study by ARDS Network found similar outcomes using CVP vs. PAOP to guide management of ARDS patients. (See [page 3-66](#) under Treatment of ARDS.)

Optional devices: Trials/developments of noninvasive hemodynamic monitoring are ongoing, such as echocardiography, tissue tonometry, surface impedance plethysmography, and esophageal and tracheal sensors that give cardiac output readings.

Know [Table 3-14](#) and know the following hallmarks:

- Hallmark of **hypovolemia**: low wedge pressure. This low LV preload → low stroke volume → low CO (once HR is maxed out; $CO = HR \times \text{stroke volume}$) → high SVR. Treat by giving fluid.
- Hallmark of **cardiogenic shock**: Low CO (i.e., the pump ain't working) → high wedge pressure (pump backs up) and increased SVR.
- Hallmark of **distributive shock**: Loss of SVR → initially low wedge pressure → initially have high CO (e.g., "warm" septic shock), which becomes low with shock progression. Treat septic shock by implementing all of following:
 - Remove source and treat with antibiotics.
 - Give fluids.
 - Give vasopressors (to increase SVR).
 - Know that this is the **only** subset of shock in which the SVR is low. In all other cases, the high SVR is the only thing keeping blood pressure high enough to sustain life.

- Hallmark of **obstructive shock**: Low filling pressure → low wedge pressure → low CO → high SVR. Treat by resolving the obstructive problem +/- fluids.

By the way, tension pneumothorax causes torsion of the heart and increased intrathoracic pressure. Torsion of the heart → twisting the great vessels, thereby causing obstruction. Increased intrathoracic pressure → decreases venous return, also causing obstruction.

SLEEP-DISORDERED BREATHING

OVERVIEW

There are various types of abnormal respiratory patterns that may occur during sleep. These vary from apnea (with obstructive and/or central origins) and hypopnea to "respiratory effort-related arousals."

Apnea is defined as cessation of breathing for > 10 sec (usually 20–30 sec) during sleep. It becomes clinically significant at 10–15 episodes per hour, and severe cases may have > 40 per hour. Oxygen saturation usually decreases by > 4% during the apneic episodes. The 2 main classes of sleep apnea are central and obstructive, although it can also be a combination of both.

Hypopnea is a decrease of at least 30% of baseline air-flow with oxygen saturation usually decreasing by $\geq 4\%$.

Respiratory effort-related arousals relate to multiple arousals from sleep due to obstructive symptoms.

Patients may have daytime hypersomnolence. When severe, **pulmonary hypertension/cor pulmonale** (from the chronic hypoxia) and personality changes may develop.

Diagnosis is confirmed only by **polysomnography** (sleep study). The patient is hooked up to multiple electronic gadgets (ECG, EEG, EMG, oximeter, tidal CO₂ recorder) during sleep. Presence or absence of inspiratory effort during the apneic episode differentiates between obstructive and central apnea. O₂ desaturation to < 85% or of > 4% is significant. The frequency of hypoxic apneic episodes determines the severity of the disease. Normal is < 5–10/hr; mild is 5–20/hr; moderate is 20–30/hr; and severe disease is > 30/hr (again, various definitions).

Table 3-14: Catheterization and Shock

PA Cath: Hemodynamic Subsets of Shock

Type	CO	Wedge	SVR
Hypovolemic	Low	<u>LOW</u>	High
Cardiogenic	<u>LOW</u>	High	High
Distributive†	High-NI-Low	Low	<u>LOW</u>
Obstructive‡	Low	Low	High

†Distributive as seen in sepsis, spinal, and anaphylactic shock—have total loss of SVR.
‡Obstructive as in massive PE or tension pneumothorax. From John Morrissey, MD

Quick Quiz

- Discuss the potential complications of pulmonary artery catheters.
- A patient presents with *E. coli* sepsis. Predict cardiac output, wedge pressure, and SVR in relation to normal values. (See Table 3-14.)
- Predict PA catheter values in hypovolemic shock. In cardiogenic shock. (See Table 3-14.)
- Discuss the causes of obstructive sleep apnea.
- What should be avoided in patients with OSA?
- Describe the obesity hypoventilation syndrome and how it relates to OSA.

OSA

Obstructive sleep apnea-hypopnea (OSA) is sleep apnea or hypopnea occurring despite continuing ventilatory effort. The obstructive episode is usually followed by a loud snore. Patients have daytime hypersomnolence and snoring, and may have headaches, and recent weight gain.

OSA is frequently associated with an abnormal upper airway, myxedema, and obesity (but **none** of these, including obesity, is a **necessary** feature). Causes of an abnormal airway include tonsillar hypertrophy or lymphoma, micrognathia, acromegaly, goiter, and TMJ disease.

Know that OSA is associated with several severe disease states including:

- Hypertension
- Coronary heart disease
- Stroke
- Arrhythmias

Perioperative complications and motor vehicle accidents also are common in these patients. Patients with untreated, severe disease and those who are untreated with CHD have decreased survival.

Treatment of OSA

Treat the most persistent and significant OSA with either nCPAP or bi-level PAP. With nCPAP (nasal continuous positive airway pressure), air at constant pressure (5–15 cm H₂O) is supplied via a well-sealed nose mask. This “splints” the pharynx open at night. It is **very effective**. BiPAP (bi-level positive airway pressure) is similar but can be used with a nasal or full face mask and allows independent adjustment for inspiratory and expiratory pressures. This improves comfort and compliance.

You can often treat **mild-to-moderate** OSA successfully with weight loss, avoiding alcohol/sedatives/hypnotics, and not sleeping in the supine position. Nasal and intraoral patency devices may also help.

Treat **moderate** OSA with **uvulopalatopharyngoplasty** and/or either nCPAP or bi-level PAP. Uvulopalatopharyngoplasty often eliminates the snoring, but, overall, it **cures** only 50% of OSA. It is most effective in young, thin patients with mild-to-moderate obstructive sleep apnea and in those with certain specific sites of obstruction. It is sometimes used in severe sleep apnea to decrease the amount of PAP required.

Severe OSA may require tracheostomy, which is effective.

Modafinil (Provigil®) is used if the patient is getting daytime sleepiness despite receiving full therapy as discussed above.

The tricyclic protriptyline is used with varying success.

OHS

Obesity hypoventilation syndrome (OHS; Pickwickian syndrome) is defined as hypoventilation while awake, and **most** also have **OSA**.

Patients with OHS have 2 main findings:

- 1) BMI > 35 kg/m² in most
- 2) pCO₂ > 45 mmHg when awake

If no ABGs are available, look for an elevated bicarbonate on the serum chemistry as a clue (due to compensation for the chronic respiratory acidosis).

Treatment: The aim of therapy is to decrease obesity and increase ventilatory drive. Patients should lose weight. **Progestins** are respiratory stimulants and help with daytime symptoms but do **not** benefit concurrent OSA. OSA must be addressed separately. Treatment for the OSA may benefit the OHS.

CSA SYNDROME

Central sleep apnea syndrome (CSAS) occurs in < 5% of sleep apnea patients. Cheyne-Stokes breathing is a type of central apnea and is usually seen with CNS disease, but it frequently occurs in healthy persons when they're at high altitudes for the 1st time and is also seen in patients with CHF. Ondine's curse is a very rare syndrome, in which breathing is a voluntary function only.

Treatment of CSAS: Avoid CNS depressants, such as alcohol, sedatives, and hypnotics. Weight loss and avoid sleep deprivation.

Mild CSAS treatment is not standardized. Try different therapies. Supplemental nighttime oxygen has been helpful for those with hypoxemia. **Acetazolamide** is often helpful; it causes a metabolic acidosis that stimulates a central compensatory response. Theophylline is also being studied.

Nasal CPAP or even bi-level PAP may be useful—they are thought to decrease frequency of apneas by propping open airways that might be narrowed or closed with the apneic episodes. Note that nCPAP and bi-level PAP are also useful in patients with Cheyne-Stokes breathing.

Question: When do nocturnal O₂ desats occur **without** apnea? Answer: COPD/emphysema, kyphoscoliosis, and muscular dystrophy.

LUNG CANCER

NOTE

Lung cancer is the #2 cancer among men (after prostate); and the #2 cancer among Caucasian/American Indian/Alaskan native women (after breast); and #3 in African-American and Hispanic women (after breast and colorectal).

Lung cancer is the **leading cause of cancer-related death** in men and women (except Hispanic women, in whom breast cancer is the leading cause of death).

85% of lung cancers are linked to smoking! The **risk** decreases after smoking is stopped and continues to decrease for as long as the patient remains smoke free, but the risk never returns to the baseline risk of a person who has never smoked. Lung **function** also improves after smoking cessation—but **not** to normal.

RISK FACTORS FOR LUNG CANCER

With significant asbestos exposure alone, risk of lung cancer is 6x normal; with smoking alone, it is **10x normal**. With asbestos and smoking, the risk is **60x normal** (synergistic). Asbestos is associated with the 2 most common lung cancers: adenocarcinoma and squamous. There is also an increased incidence of lung cancer with uranium and nickel mining and exposure to hexavalent chromium and arsenic. Heavy doses of radon in underground miners are associated with lung cancer, but home/office exposure as a cause is controversial.

Atmospheric pollution is a risk factor for lung cancer. Second-hand smoke in childhood (> 25 pack years) increases the chance of lung cancer in adulthood. Non-filter cigarettes are worse than those with filters. There is a definite genetic factor in susceptibility.

Malignant mesothelioma is associated with asbestos, but **not** with **smoking**. It is usually considered **pathognomonic** for asbestos exposure. Note that the death rates from mesothelioma are lower for smokers than non-smokers (!) ... because the smokers often die of another lung cancer first! It usually presents with pleuritic chest pain and a unilateral hemorrhagic pleural effusion.

Silica, when it causes silicosis, is considered a carcinogen.

TYPES OF LUNG CANCER

There are 4 major categories of cancer (shown with proportion of incidence):

- 1) Adenocarcinoma (1/3)
- 2) Squamous cell (1/3)

3) Small cell (1/4)

4) Large cell (1/5)

(hASSLe: 1/3, 1/3, 1/4, 1/5—Lung cancer is a “hASSLe”!)

Adenocarcinoma just beats out squamous cell as the most common lung cancer.

Squamous and small cell cancers are usually **central** lesions (**S-S-SENTRAL**). Adeno and large cell are **peripheral**.

Nowadays, lung cancer is discussed as small cell and non-small cell (**NSCLC**). NSCLC collectively represents adeno (with bronchoalveolar subclass), squamous, and large cell.

NSCLC

Adenocarcinoma is usually peripheral and is usually found incidentally. Adenocarcinoma metastasizes **early**, especially to the CNS, adrenals, and bones. It usually presents as a **solitary** nodule. A “bronchoalveolar carcinoma” is a subclass of adenocarcinoma that may produce a large amount of frothy sputum; it has the **least** association with smoking and a strong association with pulmonary scars (as in IPF). In severe cases, the chest x-ray is indistinguishable from ARDS.

Squamous cell cancer, unlike adenocarcinoma, does **not** metastasize early. It usually is a central/hilar lesion with local extension and often presents with obstructive symptoms (atelectasis, pneumonitis), and occasionally (7%) presents as a thick-walled (> 4 mm) cavitation. Squamous cell lung cancer is by far the most likely lung cancer to **cavitate**.

Large cell cancer is usually a peripheral lesion and tends to metastasize to the CNS and **mediastinum** (may cause hoarseness or **SVC** syndrome).

If there is a history of **asbestos** exposure, think of squamous cell cancer, adenocarcinoma, and mesothelioma.

See **Image 3-25** and **Image 3-26**.

In June of 2012, the American College of Chest Physicians, in collaboration with several societies, published a set of guidelines that recommend low-dose CT scanning as a method for lung cancer screening.

They recommend annual screening with low-dose CT only to patients who are between 55 and 74 years of age, have smoked ≥ 30 pack years, and who are either current smokers or have quit within the past 15 years. Additional caveats to those who should be screened include:

- The patient should be counseled about the potential for a false positive screening test—what it entails, including risk of harm and excess cost, as well as benefits. The greatest potential harm is the identification of nodules that end up being benign but may result in invasive procedures, such as bronchoscopy, needle biopsy, thoracoscopy, mediastinoscopy, and thoracotomy. Many patients who were diagnosed

Quick Quiz

- List some risk factors for development of lung cancer besides smoking cigarettes.
- Which lung cancers are usually central in the chest?
- Which lung cancers are usually peripheral?
- Which lung cancer is most likely to cavitate?
- For patients with a lung mass and palpable cervical lymphadenopathy, what procedure is useful for diagnosis?
- How sensitive are pleural fluid analyses for diagnosing lung cancer?

with a nodule as a result of screening also reported significant “psychological distress.”

- Patients should be screened only if the screening can occur at a multidisciplinary facility that can coordinate the CT scan along with interpretation, management of findings, and treatment of results.

Younger patients who do not smoke as much should not undergo any form of screening.

NSCLC: Diagnosis and Staging

First, do a careful H+P and lab tests—CBC, calcium, bilirubin, AST, ALT, and alkaline phosphatase.

Then, order a contrasted CT scan of the chest, abdomen, and pelvis to assess the lungs, liver, and adrenals. Further imaging, such as CT/MRI of the brain, PET scan, and bone scans, depends on the results of a full review of systems, physical exam, labs, and chest/abd/pelvis CT.

Then get tissue for diagnosis.

Many different procedures exist to get lung tissue: different types of bronchoscopy, image-guided percutaneous needle biopsy, mediastinoscopy, etc. The procedure of choice is based on location of the lesion, need to assess other areas (local lymph nodes), and patient comorbidities/tolerance for procedures.

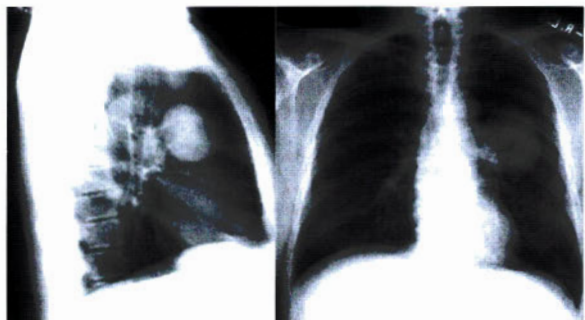


Image 3-25: Chest PA/Lat: LUL lung mass

Nowadays, the combination of imaging studies (including PET scans) and transbronchial procedures are making invasive diagnostics unnecessary.

Know: If a patient has palpable supraclavicular or cervical lymphadenopathy, fine needle aspiration or excisional biopsy helps with both diagnosis and staging and is noninvasive.

Pleural effusion cytology is helpful in staging, if an effusion is present. If the 1st sample does not show malignant cells, submit a 2nd (diagnostic yield > 90% on 3 samples if malignancy is cause of effusion). Closed pleural biopsies are no longer needed to diagnose cancer.

The approach differs based on patient-specific parameters. Know that after imaging, you want tissue of the primary tumor for diagnosis, unless you can get diagnosis and staging done in a single procedure using lymph nodes. Aim to biopsy the safest site that will give you both a diagnosis and the most advanced stage, so that only 1 procedure will need to be done.

For NSCLC, there are 4 newer staging categories used in conjunction with the TNM staging criteria of the past (although the specifics of TNM have also recently been revised):

- 1) Clinical stage (cTNM)
- 2) Surgical-pathologic stage (pTNM, includes clinical info plus surg-path data). Clinical and surg-path staging agree only 50% of the time. Obviously, surgical staging is most definitive.)
- 3) Retreatment stage
- 4) Autopsy stage

This 7th edition TNM staging system describes **tumor**, **node**, and **mets** (updated 2009):

T indicates primary tumor size:

- T1 is < 3 cm (with subsets).
- T2 is > 3 but ≤ 7 cm or tumor involves main bronchus but ≥ 2 cm distal to carina or invades visceral pleura or is associated with atelectasis/obstructive pneumonitis and extends to hilum but does not involve entire lung (with subsets).

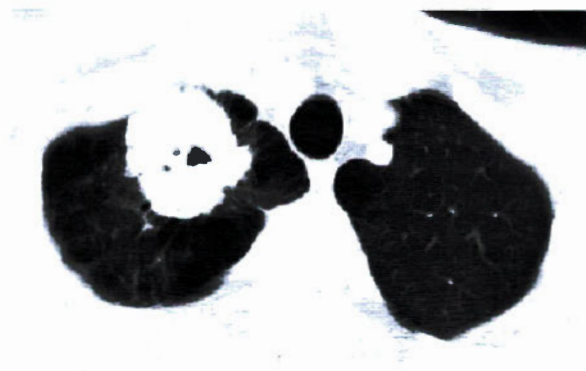


Image 3-26: CT Chest: Upper lobe lung mass

- T3 is > 7 cm or invades the chest wall, diaphragm, or phrenic nerve, mediastinal pleura, pericardium, main bronchus < 2 cm from carina; or is associated with atelectasis/obstructive pneumonitis of entire lung; or exists as separate nodules in same lung lobe.
- T4 is tumor of any size that invades major structures (mediastinum, heart, esophagus, vertebrae) or exists as separate nodules in ipsilateral but different lung lobes.

Lymph node involvement:

- N0 = none
- N1 = ipsilateral peribronchial and/or ipsilateral hilar nodes
- N2 = ipsilateral mediastinal and/or subcarinal nodes
- N3 = contralateral nodes or ipsilateral supraclavicular nodes

Metastases:

- M0 = absence
- M1 = presence (with subsets); includes malignant pleural/pericardial effusions and tumor nodules in the contralateral lung

Treatment of NSCLC Lung Cancer

- Stage I disease is defined as T1–T2a with N0, M0.
- Stages I–III patients are treated with surgery, chemo, and radiation with intent to cure.
- Stage IV disease is defined as any T, any N, with M1. Treatment of Stage IV disease is palliative.
- Most patients present with Stage III or IV disease, so 5-year survival rate is only 10–15%.

Stage I and II patients are treated with lobectomies when possible. Post-resection radiation reduces the rate of local recurrence but does not appear to affect survival.

Radiation is an alternative for non-surgical candidates.

Adjuvant treatment using **platinum**-based doublet chemo is given to Stage Ib and II because it does improve survival in these groups.

Post-treatment surveillance should include an exam with x-ray 4x/year x 2 years, then twice yearly through year 5, then annually. Substitute a chest CT for 1 x-ray yearly.

Small Cell Lung Cancer

Small cell cancer is extremely aggressive, so its treatment is usually discussed separately from the others. Contrary to other lung cancers, cavitation never occurs. Small cell lung cancer can cause SIADH, ectopic ACTH production, and Eaton-Lambert syndrome.

Small Cell: Diagnosis and Staging

Compared to NSCLC, small cell lung cancer is just **bad** disease. The tumor grows fast and metastasizes early. Small cell is more often associated with paraneoplastic syndromes (e.g., Eaton-Lambert) and ectopic hormonal syndromes (e.g., SIADH).

Most patients present with advanced disease, and the tumors do not respond as well to treatment as NSCLC. The staging system that is most useful is the Veterans Affairs Lung Study Group (VALSG), where the patient has “limited disease” if tumor is confined to the ipsilateral hemithorax or “extensive disease” if tumor has metastasized outside of the ipsilateral hemithorax. Up to 70% of patients present with “extensive” disease.

Diagnosis requires a good physical exam and review of systems, x-ray, and chest CT. Once tissue is obtained for diagnosis, lots of imaging studies are performed (contrasted CT of head, abdomen, pelvis, bone scan, and marrow biopsies, if indicated).

Know that small cell lung cancer is rapid-growing (usually all symptoms evolve within 8 weeks prior to diagnosis), so you absolutely cannot delay staging a patient more than a **week** after diagnosis—because the patient can get real sick really quickly.

Treatment of Small Cell Lung Cancer

Survival periods for majority of small cell lung cancer patients (and 5-year survival rates):

Limited disease = 15–20 months (10–13%)

Extensive disease = 8–13 months (1–2%)

For small cell cancer, use chemotherapy, radiation therapy, or occasionally adjuvant surgery. Because of the poor prognosis, all treatment for small cell cancer is only palliative.

SOLITARY PULMONARY NODULE

The “**solitary pulmonary nodule**” is a nodule in the middle-to-lateral 1/3 of the lung, surrounded by normal parenchyma. 35% are malignant.

Most solitary pulmonary nodules are found on chest CT and require rescanning with CT at intervals. **Size** of the nodule **and** patient’s **risk for lung cancer** determine whether to follow the nodule with several scans at intervals or to take it out.

When a nodule is > 1–2 cm in diameter, a PET scan will usually be done prior to surgery to help with diagnosis and staging.

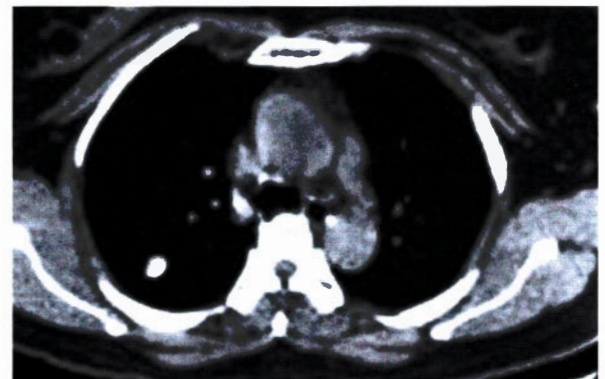


Image 3-27: CT Chest: calcified pulmonary nodule

Quick Quiz

- Define Stage I non-small cell lung cancer.
- Characterize the course of patients with small cell lung cancer.
- What type of calcifications indicate a benign solitary pulmonary nodule?
- What do you do with the solitary pulmonary nodule in the patient with risk factors for cancer?
- Which lung cancers are associated with SIADH? With hypercalcemia? With gynecomastia? With HPO?
- List causes of superior vena caval syndrome, both malignant and non-malignant.
- What are the most common causes of anterior mediastinal masses? Posterior? Middle? (See Table 3-15.)

Calcification of a solitary pulmonary nodule suggests it is benign. It is virtually always benign if the calcification is “popcorn” (hamartoma), laminated (“bulls eye” = granuloma), or has multiple punctate foci or dense central calcification (Image 3-27).

In low-risk patients (e.g., age < 35 and a nonsmoker), it is acceptable to follow a solitary calcified nodule with chest x-rays q 3 months. It is considered benign if, after 2 years, there is no growth. There is still controversy regarding semi-solid nodules, and most feel that a follow-up of 4–5 years for stability is required due to the risk of bronchoalveolar cell carcinoma.

High-risk patients **require** a diagnosis. This can be accomplished using any of the following:

- Fine needle aspiration (must be able to hit the center of the nodule; 10–15% risk of pneumothorax).
- Bronchoscopy (won’t reach peripheral lesions).
- Surgical lobectomy (can remove the nodule at the same time).

- If nodules are > 1-cm diameter, 5-fluorodeoxyglucose + PET scan may also be able to sort out benign from malignant lesions.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes (favorite topics for Board questions) occur in ~ 2–20% of lung cancer patients:

- Hypercalcemia (from PTH-secreting cancer) is associated with **squamous** cancer (think sCa++mous!). The calcium level is proportional to the tumor bulk. Hypercalcemia is seen less often in **large** cell (12%).
- SIADH, ectopic ACTH production, and Eaton-Lambert syndrome are associated with small cell cancer. (Wow, small cells do all that?) Note: Diabetes insipidus is not a paraneoplastic syndrome. If a patient presents with this and a lung cancer, consider brain metastases!
- Gynecomastia is associated with **large** cell cancer.
- Hypertrophic pulmonary osteoarthropathy (HPO) is especially associated with **adenocarcinoma**, but it is seen in all 3 NSCLC types. With HPO, patients get clubbing and new bone formation on the **long** bones, which appear **dense** on x-rays. These patients often present with only painful ankles and clubbing.

SVC SYNDROME

Superior vena caval syndrome. 85% of malignancy-associated cases are caused by **small cell** or squamous cell lung cancers (less often, lymphoma and metastatic tumors). Permanent central venous access is an emerging cause.

Presentation includes swelling of the neck and face (especially the periorbital region), shortness of breath, and cough. Exam is very significant: distended neck veins with visible collaterals, edema across the chest onto the face, and difficulty breathing. Hypotension may also be present.

Diagnosis is usually obvious by looking at the patient. Contrasted CT is the recommended imaging. If the patient does not already carry a diagnosis of malignancy, and

Table 3-15: Mediastinal Masses — Type Based on Location

Anterior		Middle	Posterior
1) Thymoma	6) Aortic aneurysm	1) Lymphoma	1) Neurogenic tumors
2) Thyroid tumor	7) Lymphoma	2) Cysts	2) Gastroenteric cysts
3) Parathyroid tumor	8) Thymus	3) Lymphadenopathy	3) Esophageal lesions
4) Teratoma	9) Other endocrine tumors	4) Aortic aneurysm	4) Aortic aneurysm
5) Lipoma		5) Hernia	5) Hernia

Of the primary mediastinal tumors:

20% = Cysts

20% = Neurogenic tumors

20% = Thymomas*

10% = Lymphomas

10% = Teratomas

20% = Miscellaneous

*Note that the thymomas are associated with autoimmune diseases, such as myasthenia gravis.

the chest CT does not show one, go look for it. Tracheal obstruction is the concern.

Treat less acute cases with diuretics and elevation of the head. Steroids help reduce tumor size only in lymphomas. Radiation helps NSCLC and other solid tumor mets. Chemo helps small cell lung cancers. Needless to say, all of these interventions are strictly palliative.

In the rare case where the cause of SVC is non-malignant (e.g., aortic aneurysm, goiter, benign tumors), surgery on the underlying condition can help. If the cause is venous thrombosis due to an indwelling central venous catheter, the catheter should be removed and the patient should be anticoagulated.

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Nephrology

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RENAL TESTS

URINALYSIS (U/A)

Proteinuria is the best indicator of underlying renal pathology. Normal 24-hour urine protein is < 150 mg. Greater than 2.5–3.5 g/d (or 40–50 mg/kg/d) indicates significant glomerular pathology. Patients with proteinuria < 1 g/d are more likely to have interstitial renal disease. **Medullary cystic disease** and **obstructive uropathy** are the only exceptions in which there can be pathology and a **normal urine sediment** with minimal proteinuria. Know that the production of light chains in some cases of myeloma is not picked up on urine dipstick, and also know the causes of false-positive urine albumin on dipstick: very alkaline urine with a pH > 8, fever, heart failure (HF), urinary tract infection (UTI), and very concentrated urine.

Transient proteinuria is common in people during a febrile illness, after strenuous exercise, and in patients with HF and COPD. Recheck urine when the acute situation has passed. If the repeat urinalysis is negative, the condition can be considered benign. There is an entity called **benign orthostatic proteinuria**, in which the proteinuria reverts to near-normal values when the patient is supine.

Spot protein:creatinine ratio is a simpler method to determine proteinuria because it requires only a random urine sample for these 2 values. The ratio of the protein:creatinine equates roughly to the gram amount of protein in a 24-hour urine (i.e., a protein:creatinine ratio of 3.5 = a 24-hour urine of 3.5 gm). This test has become the recommended test to determine and follow proteinuria in patients with renal disease. Proteinuria ranges, using spot ratio:

- < 0.15 (150 mg) = normal
- 0.03–0.3 (30–300 mg) = microalbuminuria
- 0.3–1 = overt proteinuria, usually due to interstitial disease
- 2.5–3.5 = nephrotic range
- Microalbuminuria is the earliest indicator of diabetic and hypertensive nephropathy—and is too small to be detected on the urine dipstick.
- RBC casts or “dysmorphic” RBCs indicate probable glomerulonephritis. When there are no RBCs on microscopic analysis, but the urine dipstick is positive, think of hemoglobinuria or myoglobinuria. One unusual cause of hemoglobinuria is lysis of RBCs in very dilute urine.
- With eosinophiluria, think of drug-induced interstitial nephritis.

SERUM CREATININE

Creatinine is the common screening measure of renal function but varies depending on the amount produced by muscle tissue. The more muscle tissue one has, the higher the creatinine. Also, if muscle tissue breaks down

(as in rhabdomyolysis or myositis), creatinine values can rise acutely. With aging, there is less muscle mass, and the creatinine does not rise despite reduced renal function.

Serum creatinine (sCr) is artificially **increased** by cimetidine, probenecid, and trimethoprim. These drugs decrease the tubular secretion of creatinine (elevating the serum value), but true glomerular filtration is not affected. Acetone and cefoxitin interfere with the test for creatinine and may give falsely elevated results. An elevated (> 20:1) BUN:Cr ratio indicates either pre-renal azotemia (low flow and increased absorption) or increased protein breakdown. The increased protein breakdown can be due to increased protein intake, GI bleed, total parenteral nutrition (TPN), catabolic states, or steroids that increase protein turnover.

GFR

Glomerular filtration rate (GFR) is the most accurate way to measure stable renal function. While GFR has been traditionally calculated as the creatinine clearance (CrCl) in mL/min = UV/P , where UV is the total urine creatine/24 hours divided by the serum creatinine (sCr), the most accurate method in patients with impaired renal function is to calculate GFR using the following modification of diet in renal disease (MDRD) formula. MDRD needs only serum values and accounts for race, sex, age, and nutritional status. A program for this calculation is available online.

The **Cockcroft-Gault formula** is another acceptable way to estimate GFR as CrCl =

$$[(140 - \text{age}) \times (\text{Wt}) \times (0.85 \text{ if female})] / (72 \times \text{sCr}) \quad [\text{eq 1}]$$

$$[\text{CrCl} = \text{mg/min}; \text{age} = \text{years}; \text{wt} = \text{kg}; \text{sCr} = \text{mg/dL}]$$

FE_{Na}

The fractional excretion of sodium (FE_{Na}) is a measurement of excreted Na⁺ over the total filtered load of Na⁺. It is most useful in evaluating oliguric acute kidney injury and is primarily used to differentiate prerenal azotemia from acute tubular necrosis (ATN).

- Prerenal azotemia = FE_{Na} < 1%
- Acute tubular necrosis = FE_{Na} > 2%

Contrast-induced ATN is an exception, where the FE_{Na} can be < 1%.

$$\text{FE}_{\text{Na}}(\%) = (\text{sCr} \times \text{uNa}) / (\text{uNa} \times \text{uCr}) \times 100 \quad [\text{eq 2}]$$

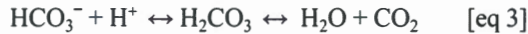
RENAL BIOPSY

Biopsy is used to diagnose unexplained causes of acute renal failure, nephrotic syndrome, and glomerulonephritis. In transplant patients, it assists in distinguishing between medication toxicity, ATN, viral infections, and acute rejection.

ACID-BASE DISORDERS

MECHANISMS

There is really only one chemical equation you **must** know to calculate and understand all acid-base problems. This is the Henderson-Hasselbalch equation. It is derived from the bicarbonate buffer equation shown here:



HCO_3^- is bicarbonate. H_2CO_3 is carbonic acid. CO_2 is carbon dioxide. These 3 molecules are in equilibrium with one another. From the above equation is derived the Henderson-Hasselbalch equation. (Derivation is shown in appendix A at the end of this section.)

$$\text{pH} = \text{pK} + \log (\text{HCO}_3^- / [0.03 \times \text{P}_a\text{CO}_2]) \quad [\text{eq 4}]$$

...which can be more easily used as:

$$\text{H}^+ = 24 \times (\text{P}_a\text{CO}_2 / \text{HCO}_3^-) \quad [\text{eq 5}]$$

This equation tells us that the body has only 2 ways to control the serum pH:

- 1) Regulate the respiratory rate and tidal volume; thus, control the P_aCO_2 .
 - 2) Regulate the kidney's reabsorption of HCO_3^- .
- It further shows that it is the ratio of P_aCO_2 to HCO_3^- that determines pH and not the absolute levels.

Disorders that affect pH are acid-base disorders. Primary acid-base disorders are either respiratory or metabolic in origin:

- Primary respiratory disorders: The change in P_aCO_2 causes the initial change in pH; and the kidney **slowly** responds in an opposite direction by dumping or holding on to HCO_3^- .
- Primary metabolic disorders: The change in HCO_3^- causes the initial change in pH; and the respiratory rate **immediately** increases or decreases.

Again: The kidneys respond **slowly** to changes in pH while the respiratory rate responds **immediately**.

We will soon go over a quick and more exact method of calculating acid-base status; but first, let's discuss anion gap, osmolal gap, and causes of acid-base abnormalities.

Remember: Significant alkalemia of any etiology can cause the diffuse paresthesias/numbness and muscle spasms we usually associate with acute hyperventilation; the high pH increases the fraction of bound calcium. The resulting decrease in ionized calcium produces these symptoms of hypocalcemia. There is no change in total serum calcium (ionized + bound). This effect also can

be induced by rapid overload with intravenous HCO_3^- or with citrate (massive blood transfusion).

ANION GAPS

Serum Anion Gap

The serum anion gap, simply called "anion gap" (AG), is **always** determined using measured ions found in the chemistry panel.

$$\text{AG} = \text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-) \quad [\text{eq 6a}]$$

Alternatively, you can use:

$$\text{AG} = [(\text{Na}^+ - \text{HCO}_3^-) - \text{Cl}^-] \quad [\text{eq 6b}]$$

These are the same formula. Regardless of which way you use it, be very certain about your order of operations, so you get the correct value. Note that K^+ is left out. This is because it doesn't change enough to affect the gap. The normal AG values already reflect a normal K^+ level.

Table 4-1 describes how a normal anion gap is generated. The AG is a determination of unmeasured anions, which, when elevated, indicates an increase in unmeasured **acids**. Why is this? Because most of the chemicals that add extra anions to the blood in a pathologic fashion are acid (e.g., ketoacids, lactate, ethylene glycol, methanol). And these acids are composed of an unmeasured anion with a positively charged hydrogen, H^+ (which decreases pH).

Normal values for the AG vary depending on the lab you use. Typically, normal is 10 ± 3 (i.e., 7–13), and these are the values used in this section.

Under normal conditions, albumin is the main contributor to the AG; therefore, hypoalbuminemia can give a falsely low AG (~2.5 mEq/L decrease in the AG for each 1 g/dL decrease in albumin).

Always calculate the AG when presented with acid-base and electrolyte problems. As shown in Table 4-1, an **elevated** anion gap means an increased $[\text{H}^+]$, which **always** means metabolic **acidosis**. When metabolic acidosis occurs with a high AG, it is called High AG Metabolic Acidosis or HAGMA.

When metabolic acidosis occurs with a normal AG, it is called Normal AG Metabolic Acidosis or NAGMA.

Note: Ethanol intoxication itself does not cause an elevated anion gap, but alcoholic **ketoacidosis** does.

Urine Anion Gap

The Urine Anion Gap (UAG) is used to evaluate the etiology of NAGMA to differentiate between

Quick Quiz

- What effect does respiratory rate have on pH? How quickly does this occur?
- What is the calculation used to determine the serum osmolality? The osmolal gap?
- What substances are associated with an increased OG and normal AG?
- What substances cause both an increased AG and OG?

gastrointestinal loss of HCO_3^- and renal tubular acidosis (RTA; see [page 4-15](#)). UAG is determined using the measured ions in the urine, Na^+ , K^+ , and Cl^- , expressed in mEq/L.

$$\text{UAG} = \text{Na}^+ + \text{K}^+ - \text{Cl}^- \quad [\text{eq 7}]$$

UAG is an artificial determination of the unmeasured ions in the urine, the most important one being NH_4^+ :

- Normal value of UAG is close to 0.
- A positive UAG value suggests low urinary NH_4^+ (e.g., **RTA**).
- A negative UAG value suggests high urinary NH_4^+ (e.g., **diarrhea**).

OSMOLAL GAP

The osmolality of the blood is determined mainly by concentrations of Na^+ , glucose, and urea.

The osmolal gap (OG) helps you determine whether unmeasured osmoles are circulating in the blood (and possibly causing an acidosis). The OG is the mathematical difference between the measured serum osmolality (from the lab) and a calculated estimation of what the osmolality ought to be—if the only effective osmoles present are the normal ones (sodium, glucose, and urea).

Use the following formula to calculate the serum osmolality (sometimes 3 and 20 are used to substitute for 2.8 and 18—it makes the math easier):

$$\text{Osm}_{\text{calc}} = 2[\text{Na}^+] + \text{BUN}/2.8 + \text{glucose}/18 \quad [\text{eq 8}]$$

Subtract this value from the lab-measured serum osmolality to get the OG. Therefore:

$$\text{OG} = \text{Osm}_{\text{meas}} - \text{Osm}_{\text{calc}} \quad [\text{eq 9}]$$

$$\text{OG} = \text{Osm}_{\text{meas}} - (2[\text{Na}^+] + \text{BUN}/3 + \text{glucose}/20) \quad [\text{eq 10}]$$

Know that a normal OG is < 10 . [Table 4-2](#) contains a list of disorders that cause a high OG.

Important causes to know specifically are **methanol** and **ethylene glycol** ingestions and **propylene glycol**. Chronic kidney disease causes a high OG from retention of small solutes. Similarly, lactic acidosis and ketoacidosis cause a high OG from the accumulation of unknown small solutes and not from the actual lactic or ketoacids.

Know that **isopropyl** alcohol ingestion is **not** associated with acidosis, even though the osmolar gap is increased (so the AG is normal). Nontoxic causes of an increased OG and normal AG are mannitol, sorbitol, and glycerol.

The main use of OG is in the workup of a patient with possible acid alcohol ingestion (e.g., ethylene glycol, methanol, or propylene glycol). Especially consider these possible poisonings if the $\text{OG} > 25 \text{ mOsm/kg}$:

- Ethylene glycol is a common primary ingredient in radiator **antifreeze** solutions.
- Methanol is a common ingredient in **paint thinners** and **deicing** solutions (e.g., windshield washer fluids). Rarely, methanol is an inadvertent contaminant of “**moonshine**.” Methanol is a by-product of grain fermentation. Contamination of the entire still of liquor is avoided if the first 200 cc is discarded. This intoxication is rare.

Table 4-1: Derivation of the Anion Gap

The anions (A^-) in blood include HCO_3^- , Cl^- , phosphate (phos), sulfate, albumin, and organic acids. The cations are Na^+ , K^+ , Ca^{++} , and Mg^{++} . Because plasma remains neutral, the anions and cations must balance, or:

$$(\text{Na}^+ + \text{K}^+ + \text{Ca}^{++} + \text{Mg}^{++}) - (\text{HCO}_3^- + \text{Cl}^- + \text{phos} + \text{sulfate} + \text{albumin} + \text{organic acids}) = 0$$

This is very cumbersome so some normally unmeasured ions that stay relatively constant have been dropped, leaving only the major measured ions. Pulling these unmeasured ions out of the equation results in a gap, called the anion gap:

$$\text{Anion Gap} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$$

But, didn't we remove unmeasured anion and cations? Why is it called the anion gap? Good question! The answer is that because the unmeasured cations' concentrations rarely change much, it is easiest to just think of the AG as a measurement of the unmeasured anions (mostly albumin). Any change in this gap will be due to added anions such as ketones or lactate. So, this gap is usually taught as the “anion gap” rather than the “unmeasured anions minus the unmeasured cation gap”! The anion gap is **usually** about **10 mEq/L (+/- 3)**.

Remember that any increase in unmeasured anions always is 1:1 with the increase of H^+ —so **high AG always indicates metabolic acidosis**.

Table 4-2: AG and OG in the Obtunded Patient

Anion Gap	Osmolal Gap	Consider
High	High	Methanol and ethylene glycol. Ketoacidosis and lactic acidosis. Chronic renal failure.
High	Normal	Salicylate poisoning. Methanol or ethylene glycol ingestion after substrates have been converted to acid metabolites.
Normal	High	Isopropyl alcohol or acetone ingestion.
Normal	Normal	Think carbon monoxide poisoning—before lactic acidosis develops.

- Propylene glycol is a **solvent** used in IV lorazepam. It may cause a HAGMA + OG if the lorazepam is given as a continuous infusion.

Know that these poisons quickly convert to toxic metabolites—which don't cause an increased OG. These acidic metabolites actually cause the HAGMA. It is fairly early after ingestion when you will see both the HAGMA and the elevated OG because the initial substrate is still around as the metabolites are being formed.

High OG without acidosis (with a normal chemistry and anion gap) suggests **isopropyl alcohol** or **acetone** ingestion. **Table 4-2** gives you clues as to causes of an increased AG and OG in the obtunded patient.

The metabolite of isopropyl alcohol is acetone, which is less toxic than the original alcohol. Patients do fine with supportive care until the original ingestion is completely metabolized.

METABOLIC ACIDOSIS

Etiology

Metabolic acidosis occurs with the following:

- Overproduction of lactic acid or ketoacids
- HCO_3^- wasting (renal tubular acidosis [RTA] or diarrhea)
- Under-excretion of acid (renal failure)
- Ingestion of agents that are acids (salicylates) are metabolized to acids (methanol, ethylene glycol, paraldehyde), or cause a lactic/ketoacidosis (isoniazid and iron)

Normal Anion Gap Metabolic Acidosis (NAGMA)

NAGMA (also called “hyperchloremic” acidosis) has a commensurate increase in Cl^- with the decrease in HCO_3^- . The Cl^- is retained to maintain electrical neutrality. **Table 4-3** reviews common causes of NAGMAs and HAGMAs.

The 3 causes of NAGMA:

- Usual: **Loss of HCO_3^-** from **diarrhea** or due to **RTA**
- Increased organic acids (NH_4^+ ; e.g., patients on total parenteral nutrition)
- Inability of the kidney to excrete endogenous acids

Again, the main causes of NAGMA are **diarrhea** and **RTA**. More on RTA on [page 4-15](#).

NAGMA plus **hyperkalemia**, think Type 4 (distal) RTA.

NAGMA plus **hypokalemia** is caused by:

- GI loss (usually)
- Types 1 and 2 (proximal) RTA

On the rare occasion when you cannot distinguish RTA from diarrhea (or other GI loss of HCO_3^- , such as a urinary fistula), calculate the UAG. (See equation 8 on [page 4-3](#).) Again:

- UAG is **positive** with NAGMA due to **RTA**.
- UAG is **negative** with NAGMA due to **GI losses**.

Toluene is a common solvent in glues and paints and can cause NAGMA. Suspect toluene exposure under these conditions: glue-sniffing, use of oil-based paints, and use of varnishes in a poorly ventilated area.

High Anion Gap Metabolic Acidosis (HAGMA)

With HAGMA, **no** equivalent increase in Cl^- is observed. Because the net charge in the serum is always neutral, there must be an increase in the **unmeasured anions**.

These tests should be performed immediately in a patient with unexplained HAGMA:

- Funduscopic exam
- Toxicology screen
- Serum glucose; urine and serum ketones
- Lactic acid level
- Serum osmolality with calculation of the osmolal gap (high in methanol and ethylene glycol ingestions)
- U/A to assess for calcium oxalate crystals

Table 4-3: HAGMAs and NAGMAs

Common Causes of HAGMA

Severe CKD (CRF): decreased acid (especially NH_4) excretion—commonest
 Ketoacidosis: diabetic, alcoholic, starvation
 Lactic acidosis: drugs, toxins, circulatory compromise
 Poisonings: salicylates, methanol, ethylene glycol

Common Causes of NAGMA

Renal tubular acidosis
 Diarrhea
 Carbonic anhydrase inhibitors
 Hyperalimentation with TPN

Quick Quiz

- What are the 2 main causes of NAGMA?
- Which NAGMA is associated with hyperkalemia?
- What are the causes of HAGMA?
- What are the potential PE findings in a patient who has ingested methanol?
- What abnormality is sometimes noted in the urine of patients who have ingested ethylene glycol?
- What is the treatment for methanol and ethylene glycol ingestions?

The 4 common causes of HAGMA include:

- 1) Ketosis (diabetic, alcoholic, and starvation):
 - **Diabetic ketoacidosis (DKA):** Classic findings include volume depletion, a normal Cl^- , and HAGMA in a diabetic. DKA responds to restoration of intravascular volume, replacement of electrolytes, and control of the blood glucose. DKA is discussed in the Endocrinology section, Book 4.
 - **Alcoholic ketoacidosis (AKA):** Key clue is an alcoholic who presents with HAGMA. Classic findings include HAGMA, hypophosphatemia, and hypoglycemia in a known alcoholic. AKA responds well to dextrose infusion.
- 2) Uremia causes an accumulation of anions including sulfate, phosphate, and urate.
- 3) Lactic acidosis:
 - **Type A** is due to muscle hypoperfusion during shock, cardiac failure, or sepsis.
 - **D-lactic acidosis** can occur in patients with short bowel syndrome; they present with typical neurologic abnormalities, from slurred speech to obtundation. D-lactic acid is not the normal L-lactic acid seen with anaerobic metabolism. D-lactic acid takes much longer to break down and therefore accumulates more quickly and hangs around longer.
- 4) Toxins (salicylates, ethylene glycol [makes glycolic and oxalic acid], methanol [makes formic acid], and propylene glycol):
 - **Salicylate overdose:** Key clue is **mixed respiratory alkalosis + HAGMA**. Salicylate intoxication initially causes a respiratory alkalosis, then HAGMA. Look for a history of an over-the-counter pain medication as the key clue.
 - **Ethylene glycol:** Key clue is **calcium oxalate** crystals in the urine. Ethylene glycol forms glycolic acid and oxalic acid, resulting in HAGMA.
 - **Methanol:** Key clue is **visual symptoms**. Methanol metabolizes to formaldehyde and formic acid, resulting in HAGMA. Patients present with nausea, vomiting, abdominal pain, and may have visual

complaints described as “walking through a snow-storm.” Formic acid is toxic to the optic nerve. **Methanol** and **ethylene glycol** are toxic because of their metabolites. Like ethanol, these substances are metabolized by alcohol dehydrogenase. The previous treatment was to start an ethanol drip to act as a competitive inhibitor of alcohol dehydrogenase. Fomepizole + dialysis now make up the standard of care for both of these ingestions.

- **Propylene glycol:** Propylene glycol is used as a solvent for **intravenous lorazepam**. Continuous infusion or large IV doses of lorazepam can cause propylene glycol toxicity, which manifests as HAGMA with an osmolar gap.

METABOLIC ALKALOSIS

Metabolic alkalosis commonly results from **volume contraction** caused by diuretics or vomiting/gastric suction. HCl is lost during vomiting, but this mechanism does not generate the alkalosis. Contraction alkalosis and hypokalemia are effects of aldosterone-mediated activation of distal tubular Na^+/H^+ and Na^+/K^+ pumps. Because of the volume-contracted state, sodium absorption from urinary filtrate is increased in exchange for acid and potassium, which are lost in the urine. Also in alkalemia, there is increased cellular K^+ uptake in exchange for H^+ .

Urinary Cl^- is $< 10 \text{ mEq/L}$ because NaCl is avidly resorbed to maintain intravascular volume. If urinary Cl^- is > 10 , think of other causes of alkalosis such as Cushing syndrome, Bartter syndrome, Gitelman syndrome, primary hyperaldosteronism, severe hypokalemia, or increased intake of HCO_3^- .

Treatment is aimed at **restoration of volume** with IV fluids (with either NaCl or KCl) and interruption of the cycle causing persistent volume loss. **Potassium correction** is integral to resolving the alkalosis, as well. Both interventions interrupt aldosterone production.

The carbonic anhydrase inhibitor, acetazolamide, which increases bicarbonate excretion, can be used in patients who have alkalosis with contraindications to volume resuscitation (e.g., severe edematous states such as decompensated heart failure).

Severe metabolic alkalosis (> 7.55) can be treated with HCl , which must be infused over an extended period of time through central venous access. This is done only in severe circumstances and usually only in the ICU.

ANALYSIS OF ACID-BASE PROBLEMS

Introduction

There are several methods used for figuring out acid-base problems. Here we give you a good method to quickly crank out pretty accurate acid-base diagnoses—even oddly mixed ones.

In this topic, we use pCO_2 for P_aCO_2 . And we drop the brackets to indicate concentration of a substance. For instance, we will use HCO_3^- instead of $[\text{HCO}_3^-]$.

The Step Method of Acid-Base Analysis

Overview

The process is simple and quick. This method can easily handle multiple, concurrent acid-base disorders.

The information required to determine exactly what the acid-base status is:

- ABG: pH and $p\text{CO}_2$
- Anion gap = $\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$

The Steps

There are **4 major steps** to this method. Go through **Table 4-4** as you read the following explanations:

Step 1:

To review, remember that the body does not fully compensate for primary acid-base disorders; therefore, the pH narrows down what the primary disturbance is (assuming no treatment). If the patient has an **acidemia**, the primary disturbance is a metabolic or respiratory **acidosis**. If the patient has an **alkalemia**, the primary disturbance is a metabolic or respiratory **alkalosis**.

Serum pH < 7.35 defines acidemia.

Serum pH > 7.45 defines alkalemia.

Physiologic explanation for upcoming Steps 2 and 3: Recall from basic physiology, the body has complex buffering systems for acidosis (intracellular and extracellular systems). The main extracellular buffer is bicarbonate, and its primary job is to complex with acids to neutralize them and keep the blood pH stable. It follows, then, that for every 1 increase in an acidic anion in the blood, the bicarbonate level should reduce by 1 (because of the neutralization). (In some instances, the ratio of anions to bicarb reduction is 1.6:1, but generally 1:1 works.) The point is: As anions go up, bicarb goes down proportionally.

In Steps 2a, 2b, and 3a, we calculate the ΔAG (the difference between the calculated AG and normal), and

then determine what the expected bicarb level should be, based on any increase in AG (recognizing that bicarb should fall by 1 for every 1 increase in the AG). If there are no extra anions, then the bicarb should be normal.

Steps 2–3 evaluate the patient for a **metabolic** component.

Step 2a: AG

Calculate the anion gap = $\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)$.

Use 10 $\pm$ 3 as normal.

So, if the AG > 13 = HAGMA is present.

Step 2b: ΔAG

Calculate the change in the anion gap (ΔAG) = (Calculated AG) – 10 or $[\text{Na}^+ - (\text{HCO}_3^- + \text{Cl}^-)] - 10$.

Step 3a: Expected bicarb

Calculate the expected bicarbonate level.

If the AG is elevated, the expected bicarbonate = $[25 - (\Delta\text{AG})]$.

If the AG is not elevated, the expected bicarbonate = 25.

Essentially, what you're doing in this step is reducing the bicarbonate by 1 for every 1 acidic anion that the bicarbonate neutralizes.

Step 3b: (Expected – measured bicarb)

Compare the expected bicarbonate from Step 3a (either 25 or $[25 - (\Delta\text{AG})]$) to the actual bicarbonate from the chemistry panel.

If the **measured bicarbonate is less** than what is expected, **NAGMA** is present.

If the **measured bicarbonate is more** than what is expected, a **metabolic alkalosis** is present.

NAGMA and the metabolic alkalosis can coexist with a HAGMA. A standard deviation of 3 exists on each of these calculations, so if the calculated and observed values are within 3 numbers, call them “close enough.”

Step 4: Any **respiratory** component?

Step 4a:

Calculate the expected $p\text{CO}_2$. The expected $p\text{CO}_2$ = $15 + \text{actual } \text{HCO}_3^-$ from the chemistry.

Step 4b:

Compare the expected $p\text{CO}_2$ to the actual $p\text{CO}_2$ from the blood gas.

If **higher** than expected $p\text{CO}_2$ is present in the blood gas results, a respiratory **acidosis** is present.

If **lower** than expected $p\text{CO}_2$ is present in the blood gas results, a respiratory **alkalosis** is present.

Table 4-4: Evaluating Acid-Base Disorders

Step	Questions	How to Determine Answer
1) pH	Determine serum pH	Look at ABG results
2) Anion Gap	What is the Anion Gap?	$\text{Na}^+ - \text{Cl}^- - \text{HCO}_3^-$
	What is change in AG? (measured – normal)	AG – 10
3) HCO_3^-	What is expected HCO_3^- ?	$25 - (\text{change in AG})$
	Compare expected HCO_3^- to actual HCO_3^-	
4) $p\text{CO}_2$	What is expected $p\text{CO}_2$?	$15 + \text{measured } \text{HCO}_3^-$
	Compare expected $p\text{CO}_2$ to actual $p\text{CO}_2$	

Quick Quiz

- When looking at a blood gas result, how do you determine which acid-base disorder is the primary disturbance?
- What happens to a patient's serum bicarbonate level when acid anions accumulate in the blood?
- Know the 4-step method!

These respiratory disorders can coexist with any of the metabolic disorders. A standard deviation of 3 exists on each of these calculations, so if the calculated and observed values are within 3 numbers, call them "close enough."

Caveats

Other key points to keep in mind:

- ABG and chemistries must be drawn at the same time.
- If $\text{HCO}_3^- < 9$ or > 40 , expected pCO_2 may be unreliable.
- All of the diagnoses are independent disorders; compensation is built into the formulas.
- Always make sure the diagnosis is consistent with the clinical history.
- Look for a discrepancy between the direction of Na and Cl to signal an acid-base disorder!
- Even in chronic respiratory acidosis, the serum bicarbonate does not increase above 38 mEq/L. Also, $\text{pCO}_2 > 55$ usually suggests an additional primary respiratory acidosis.

Acid-base Example #1

Blood gas: 7.50 / 20 / 15

Na = 140, Cl = 103, Bicarb = 15

Step 1: First look at the pH. It is 7.50, which tells us our primary disorder is either a respiratory or metabolic alkalosis.

Step 2a: Calculate the anion gap.

$$140 - (103 + 15) = 22$$

Because the AG is > 10 , HAGMA is present.

Step 2b: Calculate the ΔAG :

$$\text{AG} - \text{normal AG} = (22) - (10) = 12$$

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^- . Expected $\text{HCO}_3^- = 25 - \Delta\text{AG} = 25 - 12 = 13$. Measured HCO_3^- is 15. This is close enough. No additional metabolic disorder is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = $15 + 15 = 30$. Actual pCO_2 is 20. There is less CO_2 than you expect there to be, so a respiratory alkalosis is present. This is the primary disorder because Step 1 defines the primary disorder as an alkalemia.

So, the patient has a primary respiratory alkalosis + HAGMA. This scenario is seen with salicylate poisoning. As discussed under HAGMA (page 4-4), salicylates initially increase the respiratory drive causing respiratory alkalosis; then metabolic acidosis develops.

Acid-base Example #2

Blood gas: 7.30 / 40 / 24

Na = 145, Cl = 100, Bicarb = 24

Step 1: First look at the pH. It is 7.30, which tells us our primary disorder is either a respiratory or metabolic acidosis.

Step 2a: Calculate the anion gap.

$$145 - (100 + 24) = 21$$

Because the AG is > 10 , HAGMA is present.

Step 2b: Calculate the ΔAG :

$$\text{AG} - \text{normal AG} = (21) - (10) = 11$$

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^- . Expected $\text{HCO}_3^- = 25 - \Delta\text{AG} = 25 - 11 = 14$. Measured HCO_3^- is 24. There is more bicarb than expected, so an additional metabolic alkalosis is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = $15 + 24 = 39$. Actual pCO_2 is 40. This is close enough. There are no additional respiratory disorders.

Because the patient is acidemic, the patient has a primary HAGMA + metabolic alkalosis.

Diagnosing the Cause of the Abnormal Acid-Base Status

Note: To make the diagnosis of causes of the abnormal acid-base state (discussed previously), you often need more information. This may include the following:

- Urine anion gap (if NAGMA) = $(U_{Na} + U_K) - U_{Cl}$ to differentiate RTA from GI losses (page 4-2).
- Serum K^+ to help differentiate RTAs (page 4-15).
- Osmolal gap = $Osm_{meas} - Osm_{calc}$ to help with poisonings (page 4-3).
- Salicylate levels, lactic acid level, glucose, etc.

Review Table 4-2 and Table 4-3 for causes of osmolal gaps, anion gaps, NAGMAs, and HAGMAs.

You can get pretty quick at crunching through the 4-step method above. It is also important to get an innate feel for the ABGs, so you can quickly pick up an abnormal situation. Review Table 4-5 to see what ABGs are expected with certain conditions.

Table 4-5: Examples of Abnormal ABGs

Examples ...	Acid-Base Status	pH	PCO ₂	PO ₂
Acute hyper-ventilation episode	Acute respiratory alkalosis	7.56	20	90
Acute asthma/PE/chest trauma	Acute resp alk due to hypoxia	7.56	20	50
CNS problem, chronic hyper-ventilation	Chronic resp alk w/metab compensation	7.44	25	90
COPD with chronic bronchitis	As above, but w/hypoxia	7.43	30	60
Pt in transition to respiratory failure	Normal except hypoxia	7.40	40	50
Sedative overdose	Acute resp acidosis	7.24	60	80
Resp failure from hypoxia	Acute resp acidosis w/hypoxia	7.16	70	50
Emphysematous COPD	Resp acidosis w/metabolic compensation	7.37	60	60
Bicarbonate overdose	Metabolic alkalosis w/resp comp	7.44	60	90
Sepsis, ASA overdose, renal failure ...	Metabolic acidosis w/resp comp	7.36	28	90
Assuming consistent HCO ₃ ⁻ and chloride				

FLUID AND ELECTROLYTES

OSMOLALITY AND VOLUME STATUS

Normal osmolality is usually 282 ± 2 mOsm/kg H₂O. If no osmolal gap exists from an acid alcohol ingestion, then measured osmolality should be equal to calculated osmolality, which is (roughly):

$$Osm_{calc} = 2[Na^+] + Glucose/20 + BUN/3$$

If glucose and BUN are normal, use $2 \times [Na^+]$ to quickly see if the calculated osmolality is about normal.

Antidiuretic hormone (ADH) is the common term for arginine vasopressin (AVP). ADH is a neurohypophyseal hormone that acts on the collecting duct to increase water permeability and mediate the urine concentration.

ADH levels are regulated by several mechanisms. Two that are most important are:

- **Osmoreceptors** in the hypothalamus
- **Volume** ("stretch") **receptors** in the left atrium (and possibly in the pulmonary veins) and blood vessels

The **strongest** stimulant for ADH release is significant **volume loss** resulting in hypotension; e.g., hemorrhage. This stimulates both the stretch receptors and baroreceptors. More on ADH in the Endocrinology section, Book 4.

Volume status of the patient with a sodium abnormality is **critical** in determining the treatment. In general, if the patient is **edematous**, there is volume **overload**. If the patient has the clinical signs of **volume loss**, there is a volume **deficit**. If there is neither of these, the patient is considered euvolemic.

Remember these clinical clues to hypovolemia: tachycardia, narrowed pulse pressure, orthostatic hypotension, and resting tachycardia with hypotension. Central venous pressure will be low.

HYPONATREMIA

Isotonic and Hypertonic

Low Na^+ is the most common electrolyte abnormality. It is further classified by osmolality as **isotonic**, **hypertonic**, or **hypotonic**.

The first step after discovering hyponatremia is to determine the serum osmolality:

- **Isotonic** hyponatremia is an artifactual decrease in the serum Na^+ associated with older lab instruments that miscalculated sodium in settings of high protein (e.g., myeloma) or lipids. The current standard in laboratory practice is to use ion-specific electrodes, thus eradicating this problem.

Quick Quiz

- What are the 2 important regulators of ADH secretion from the posterior pituitary?
- What causes hypertonic hyponatremia?
- For each 100 mg/dL increase in glucose over 100, how should you correct the serum sodium?
- What are causes of low-volume, hypotonic hyponatremia?
- What are causes of high-volume, hypotonic hyponatremia?
- What drugs cause SIADH?
- **Hypertonic:** Both **glucose** and **mannitol** cause an osmotic shift of water out of cells, which dilutes plasma Na^+ . Remember: For each 100 increase in glucose over 100 mg/dL, the sodium concentration decreases by 1.6.
- **Hypotonic** (see next).

Hypotonic

By far, the largest low- Na^+ subgroup is the **hypotonic** group.

The hypotonicity causes **intracellular swelling**, which may result in neuromuscular excitability, seizures, and coma—usually when the Na^+ falls **acutely** < 120 . If the sodium level decreases slowly, the cells re-equilibrate and do not swell enough to cause these symptoms. The hypotonic group is further subdivided by **volume** status: low, high, and normal.

Always think of the serum sodium as the ratio of water to total body sodium. Therefore, hypotonic hyponatremia is a **water** problem. Whenever the serum sodium is low, it means the patient has more water relative to total body sodium either from loss of sodium or true water excess.

In the patient with hypotonic low Na^+ , the **first** thing to do is assess the volume status, which is done clinically. Volume status essentially reflects total body sodium.

Hypotonic ... Low Volume

The **low-volume** patients have lost both water and Na^+ , but more Na^+ than water. This has several causes:

- Diuretics
- GI losses (vomiting and diarrhea)
- Third spacing of fluid
- Addison disease

In Addison's (primary adrenal insufficiency), both cortisol and aldosterone are deficient. The low aldosterone causes decreased active Na^+ resorption and therefore decreased K^+ and H^+ excretion. This results in **Na^+** and

water wasting and is also associated with **hyperkalemia** and **metabolic acidosis**.

Hypotonic ... High Volume

The **high-volume** hyponatremic patients usually retain water and Na^+ , but water more than Na^+ . These patients have dependent **edema** and **JVD**.

Causes of hypotonic, high-volume status include:

- Heart failure
- Cirrhosis
- Nephrotic syndrome
- Acute or chronic kidney disease

Normal treatment is restriction of **water** and **Na^+** . Avoid **lithium** and **demeclocycline** because they might decrease GFR, causing increased salt retention. Also **avoid** chronic, oral **thiazide** diuretics because they impair urinary-diluting ability. (Use only loop diuretics if needed.)

It's easy to precipitate acute kidney injury with rapid diuresis of a high-volume cirrhotic patient. Cirrhotics tend to have a low GFR, even with a normal serum creatinine. They have decreased muscle mass, so a decrease in their GFR is not necessarily reflected in their serum creatinine concentration.

Hypotonic ... Normal Volume

SIADH

The **normal-volume** patients usually have SIADH or are taking drugs that either mimic ADH or cause ADH release.

Know that pain and chronic nausea are potent natural stimulators of ADH release.

Normal volume hyponatremia can also be caused by psychogenic polydipsia (rare), hypothyroidism, and isolated glucocorticoid deficiency.

Causes of SIADH include the following:

- CNS disease (e.g., meningitis)
- Lung disease (e.g., pneumonia)
- Neoplasms (especially small cell lung cancer)
- Drugs

Most common drugs associated with SIADH:

- NSAIDs
- SSRIs
- Carbamazepine and oxcarbazepine
- Psychotropic drugs: haloperidol, amitriptyline
- IV cyclophosphamide
- Vincristine/vinblastine
- Cisplatin
- Chlorpropamide (now rarely used)
- Ecstasy (methylenedioxymethamphetamine)

Diagnose SIADH by comparing the urine and serum osmolalities. The normal response to hyponatremia would be to excrete free water in the urine; e.g., healthy patients would have a low serum osmolality and a low urine osmolality because they are making dilute urine; this is what you see in psychogenic polydipsia. In SIADH, however, the urine is inappropriately concentrated in the setting of a low serum osmolality. The patients are not excreting free water, so the serum osmolality is low, but the urine osmolality is high.

The mechanism for ADH release in moderate-to-severe hypothyroidism is decreased cardiac output, which stimulates the carotid baroreceptors. Rule out hypothyroidism and glucocorticoid deficiency in all patients with hyponatremia before making a diagnosis of SIADH because both causes can have low serum osmolalities and high urine osmolalities—indicative of SIADH. Sometimes you can't tell the difference using these tests, so look for the hormone deficiencies in everyone first, before diagnosing SIADH.

Thiazide Diuretics

Thiazides also can cause euvolemic hypotonic hyponatremia, but **not** via an ADH mechanism. These drugs directly increase water permeability and reabsorption in the **medullary collecting duct**, in addition to their effects on the **distal tubules**. These mechanisms are discussed further on [page 4-12](#), in the section on normal renal physiology. Elderly patients are highly susceptible to this effect of thiazides.

Treatment of Hyponatremia

Treatment of **nonemergent** hyponatremia (no CNS changes) is based on etiology:

- **Isotonic** hyponatremia: This is artifact and doesn't require treatment.
- **Hypertonic** hyponatremia: usually attributable to glucose or mannitol. Treating the underlying disease process (e.g., DKA) will normalize the sodium with time.
- **Hypotonic** and
 - **Hypovolemic**: normal saline to replenish deficit
 - **Hypervolemic**: fluid restriction (~ 800 cc/day) +/- loop diuretics
 - Euvolemic: SIADH is treated with fluid restriction (~ 800 cc/day). Refractory cases can be treated with an ADH receptor antagonist, such as conivaptan or tolvaptan, although these agents are expensive and are generally reserved for use in patients with severe, chronic hyponatremia with serum Na^+ < 120 mg/dL and CNS changes. Treat hypothyroidism or glucocorticoid deficiency with appropriate replacement.

If the symptoms of hyponatremia are **severe** (e.g., coma, convulsions) and the patient is not hypovolemic, treat with 3% saline along with loop diuretics; however, correction

of hyponatremia should never exceed **0.5–1 mEq/L/h** due to the risk of central pontine myelinolysis (see below).

Standard therapy: Give enough 3% saline over 8–12 hours to increase the serum sodium by 10 mEq/L. Calculate the mEq of Na^+ needed by multiplying total body water (60% of body weight—i.e., 60 L in a 100-kg person) x 10 mEq/L. In this case, 60 L x 10 mEq/L = 600 mEq. Each liter of 3% saline has 512 mEq of Na^+ , so give ~ 1 liter over 12 hours. The rate of correction should not exceed 1–2 mmol/hr. Then switch to the treatment consistent with the etiology of the hyponatremia.

Alternative: Recent data show that 100 cc of 3% saline given as an **intravenous bolus** raises the serum sodium enough to prevent further seizures. If required, 2 more boluses can be given in 10-minute intervals. 3 boluses should raise the serum sodium by ~ 6 mEq/L. This approach avoids the calculations above. When using this method, the serum sodium still should not be increased > 10 mEq/L in the first 24 hours.

Osmotic demyelination syndrome = Central pontine myelinolysis (because it is most prominent in the pons). If the sodium concentration is raised too rapidly, the cells can shrink (water rushes out of cells into the blood stream, where the solute concentration is higher), potentially causing this demyelination syndrome. This rare effect is more likely to occur in the patient with chronic, severe hyponatremia (Na^+ < 115 mEq/L for > 2 days) whose sodium is corrected rapidly. Symptoms are delayed by about a week, compared to the rise in the sodium concentration, and are usually not reversible. Presentation includes speech and swallowing difficulties, weakness or paralysis, cognitive deficits, and coma. Seizures occasionally occur.

HYPERNATREMIA

Overview

Severe hypernatremia is fairly rare but always represents a water deficit. It does not occur unless the patient is unable to get to water (debilitated or H_2O unavailable) or the thirst mechanism is defective. Unlike hyponatremia, these patients are **always hyperosmolar**, so the first step is determining volume status. **Low volume** implies water and Na^+ loss (more water than Na^+).

Treat severe hypernatremia with **normal saline** first to correct the volume deficit, and only then with hypotonic fluids to further replace the water deficit. Remember: Even normal saline, which is isotonic, is lower in tonicity than hyperosmolar serum.

The amount of free water needed in a hypernatremic patient is calculated by multiplying the total body water (60% of weight in kg) by the fractional difference between patient's Na^+ and normal Na^+ :

$$\text{Vol}_{\text{water}} = (\text{total body water}) \times ([\text{Na}^+_{\text{serum}} - 140]/140) \quad [\text{eq 11}]$$

Quick Quiz

- What endocrinopathies must be ruled out in all patients with hyponatremia?
- What is the suggested rate of correction of severe hyponatremia?
- When is osmotic demyelination syndrome most likely to occur? How do you prevent it?
- What is the usual cause of hypernatremia?
- What is the usual serum sodium in a patient with DI who has access to water?

$$\text{Vol}_{\text{water}} = 0.6 \times (\text{body weight}) \times ([\text{Na}^+_{\text{serum}} - 140]/140) \quad [\text{eq 12}]$$

So if a 100-kg patient has a serum Na^+ of 156, the amount of free water needed is 6.9 liters. This is usually given over 1–2 days, to decrease the sodium concentration, at a rate of 0.5 mEq/L/hr or 10–12 mEq/L/day.

Cellular swelling can occur from too rapid a correction of any severe hyperosmolar state, such as hypernatremia, nonketotic hyperglycemic coma, and severe uremia. (These are just the variables in the osmolality equation.) Cellular swelling can cause cerebral edema, seizures, and coma. So be careful with the fluid rate and measure serum sodium frequently.

High-volume hypernatremia: This is unusual and typically not serious. It most often occurs with mineralocorticoid excess, such as primary hyperaldosteronism. Usually, the only time a serious result occurs is after giving large amounts of sodium bicarbonate or hypertonic saline during advanced cardiac life support. Treat with loop diuretics and free water.

Normal-volume hypernatremia is most often seen in patients with diabetes insipidus (DI), who have reduced access to water (and thus become hypernatremic) but have not yet developed frank volume depletion. Typical DI patients with normal access to water have **normal** or **borderline-high** serum Na^+ levels because they are constantly drinking water (hyperosmolar and therefore always thirsty).

Think of **central DI** in the patient with high Na^+ and high urine volume who also has a history of recent neurosurgery, head trauma, or brain cancer/metastases. Otherwise, DI is usually **nephrogenic** (also called “ADH resistant”).

Nephrogenic DI can be hereditary, with most cases presenting in childhood (mutations in the vasopressin 2 receptor or aquaporin 2 genes) or due to:

- hypercalcemia (serum $\text{Ca}^{2+} > 11 \text{ mg/dL}$),
- chronic hypokalemia (serum $\text{K} < 3 \text{ mEq/L}$),

- intrinsic renal disease (especially **Sjögren** syndrome), or
- drugs (especially **lithium**).

Water Restriction Test

The **water restriction test** not only diagnoses DI but also differentiates between central and nephrogenic types. In a healthy person, when plasma osmolality increases to 295, ADH level is high and urine is maximally concentrated ($> 700 \text{ mOsm/L}$).

In **central** DI, even with water restriction, the ADH stays **low** and the urine dilute.

Treat **mild** cases of central DI with thiazides and salt restriction.

Chlorpropamide and carbamazepine can be used in cases of **partial** central DI, when desmopressin might be too potent or limited in supply. These drugs stimulate further ADH production if the patient has a partial defect.

Treat more resistant central DI with oral or intranasal desmopressin (synthetic vasopressin analog). Because the kidneys immediately respond to ADH, giving desmopressin (vasopressin analog) results in a quick increase of the urine concentration. The intranasal preparation is the most potent. Be careful to titrate the dose properly and counsel the patient to drink only when thirsty because volume overload and hyponatremia can easily occur (i.e., drug-induced SIADH).

In **nephrogenic** DI, the ADH is appropriately high, but the urine is **dilute**. Giving extra ADH does not increase the concentration of the urine. Treat nephrogenic DI with thiazide diuretics or amiloride. NSAIDs are used to treat rare hereditary forms.

Remember: SIADH (high ADH) usually presents as **hyponatremia** with normal volume. **DI** usually presents as **hypernatremia**, also with normal volume! See the Endocrinology section, Book 4, for a discussion on how to interpret graphs frequently encountered during water restriction testing.

Urine Osmolality

Urinary osmolality can range from 40–1,400 mOsm/L. To make sense of the osmolality, you must also know the **urine output** (liters/d). Multiply the osmolality $\times$ output (1 kg = 1 liter) to get total osmoles output per day. Normal is about 500. This is important in the case of a patient with high Na^+ and high urine output. If the 24-hour solute output is $> 900 \text{ mOsm}$, think of an **osmotic** cause of the hypernatremia (e.g., hyperglycemia); whereas in DI, the 24-hour osmoles are **normal**, so the urine is very **dilute**.

NORMAL RENAL PHYSIOLOGY, DIURETICS, AND RTAs

OVERVIEW

The following topics discuss aspects of normal tubular function, hormonal regulation of the tubules, and the effects of the 4 categories of diuretics (carbonic anhydrase [CA] inhibitors, loop diuretics, thiazides, and aldosterone antagonists).

After glomerular filtration, the filtrate flows through the following sections of tubules—some of which are grouped together because of identical function:

- Proximal tubule
- Loop of Henle
 - Thin descending segment
 - Thin ascending segment
 - Thick ascending segment
- Early distal tubule
- Late distal tubule and collecting tubule
- Medullary collecting duct

Refer to [Figure 4-1](#) and [Figure 4-2](#).

Know that diuretics are mentioned throughout this discussion of renal physiology. They are also covered when discussing drugs for HTN on [page 4-23](#).

PROXIMAL TUBULE (PT)

65% of Na^+ , Cl^- , and water is reabsorbed in the PT. The PT is very permeable to water, which is reabsorbed in a 1:1 fashion with Na^+ , such that the volume of filtrate is reduced along the tubule, but the concentration of Na^+ remains stable.

Solute are reabsorbed by the following:

- Counter-transport of Na^+ (into interstitium) and H^+ (into filtrate) via secondary active transport; stimulated by angiotensin II (AT II) and **inhibited** by **carbonic anhydrase inhibitors** and **thiazide** diuretics (slightly)
- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Co-transport of Na^+ , Cl^- , K^+ , glucose, and amino acids (into interstitium)
- Paracellular absorption of other solutes, such as Ca^{2+}

Regarding the first of the 4 bullets above, know that 90% of filtered HCO_3^- is reabsorbed in the PT—but the process is indirect and driven by the Na^+/H^+ counter-transport pump:

- H^+ is counter-transported into the filtrate and combines with filtered HCO_3^- to form H_2CO_3 (carbonic acid).
- Carbonic anhydrase converts $\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$.
- CO_2 is absorbed into the tubular cells and again, with the help of carbonic anhydrase, is converted to HCO_3^- .
- HCO_3^- is then reabsorbed into the interstitium.

So, for each H^+ that is secreted, one Na^+ and one HCO_3^- are reabsorbed. Although this is represented in [Figure 4-2](#), it is better explained here in the text.

Carbonic anhydrase inhibitors (acetazolamide) disrupt this entire process by reducing the availabilities of H^+ in the tubule cells and H_2CO_3 in the lumen. Then, the Na^+/H^+ counter-transporter does not have substrate. Na^+ is not absorbed and H^+ is not secreted. A mild diuresis ensues (as well as generation of a metabolic acidosis, similar to proximal, Type 2 RTA).

Know that this Na^+/H^+ counter-transporter is also affected by the **potassium concentration**:

- Hypokalemia: stimulates H^+ secretion (and thus, stimulates bicarb reabsorption) $\rightarrow$ alkalosis
- Hyperkalemia: inhibits H^+ secretion (and thus, inhibits bicarb reabsorption) $\rightarrow$ acidosis

So, when something goes wrong in the proximal tubules, clinically we can see (just look at those transport pumps to figure it out ...):

- Failure to **reabsorb** water
- Failure to **secrete acid** and **reabsorb bicarbonate** = generation of proximal (Type 2) NAGMA
- Failure to reabsorb solutes (Na^+ , Cl^- , K^+ , glucose, amino acids) = Fanconi syndrome +/- hypokalemia

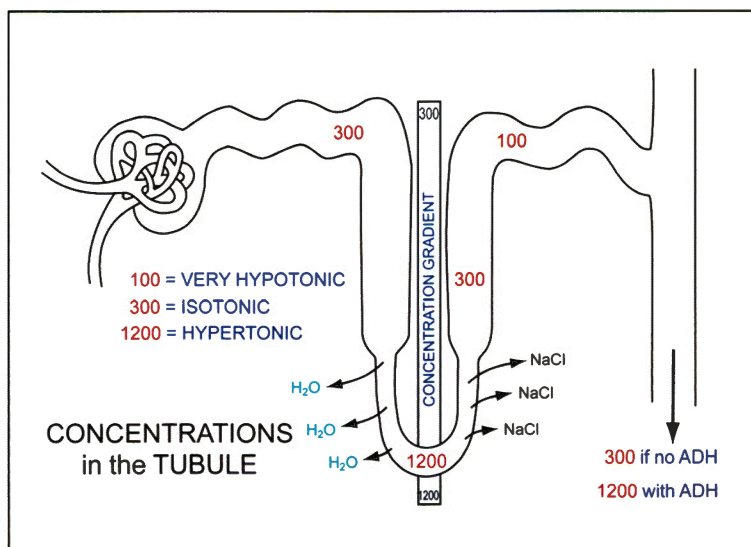


Figure 4-1: Osmolar Concentrations in the Renal Tubule

Quick Quiz

- Which tubules are permeable to water?
- Which tubule sets up the osmotic gradient for the thin, descending segment in the Loop?
- What type of diuretic is useful in patients with poor kidney function?
- Where do loop diuretics exert their effect?

LOOP OF HENLE

Follow along in [Figure 4-2](#) as we discuss the physiology of the loop of Henle. Think of the loop as divided into 2 halves with the 1st half (descending) handling reabsorption of water and a little bit of solutes, and the 2nd half (ascending) handling reabsorption of only solutes. The action of the 2nd half of the loop drives the action of the 1st half.

In the thin, descending segment, another 20% of remaining H_2O moves from the filtrate into the interstitium, following an osmotic gradient, with maximum concentration of fluid at the base of the loop. (The renal medulla is very hypertonic—*why?*) In the thin ascending segment, $NaCl$ passively diffuses into the interstitium, slightly diluting the filtrate. In the thick ascending segment, solutes are actively transported from the filtrate into the interstitium—increasing the tonicity of the medulla. (That's

why!) This active transport is the mechanism that sets up the osmotic gradient in the descending segment and stimulates reabsorption of H_2O .

In the thick ascending segment, 25% of filtrate solutes are reabsorbed by these clinically relevant processes:

- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Co-transport of Na^+ , $2 Cl^-$, and K^+ (into interstitium); **inhibited** by **loop** diuretics
- Paracellular absorption of other solutes, such as Mg^{2+} , Ca^{2+} , Na^+ , and K^+ (into interstitium)

Think about this a minute and look at the figure—be sure you understand before moving on.

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) are dose-dependent. They **remain effective** when GFR is low ($CrCl < 20$ cc/min), but you have to increase the dose and/or give IV. Ethacrynic acid is mainly used for patients with sulfa allergies in whom furosemide, bumetanide, and the thiazide diuretics are contraindicated—because these drugs are sulfa derivatives. Know that furosemide and ethacrynic acid are associated with permanent ototoxicity at high doses.

Loop diuretics cause diuresis by preventing reabsorption of Na^+ in the thick ascending segment—but also by preventing development of the interstitial osmotic gradient, relied upon by the thin descending segment for water reabsorption. The net effect is loss of both Na^+ and

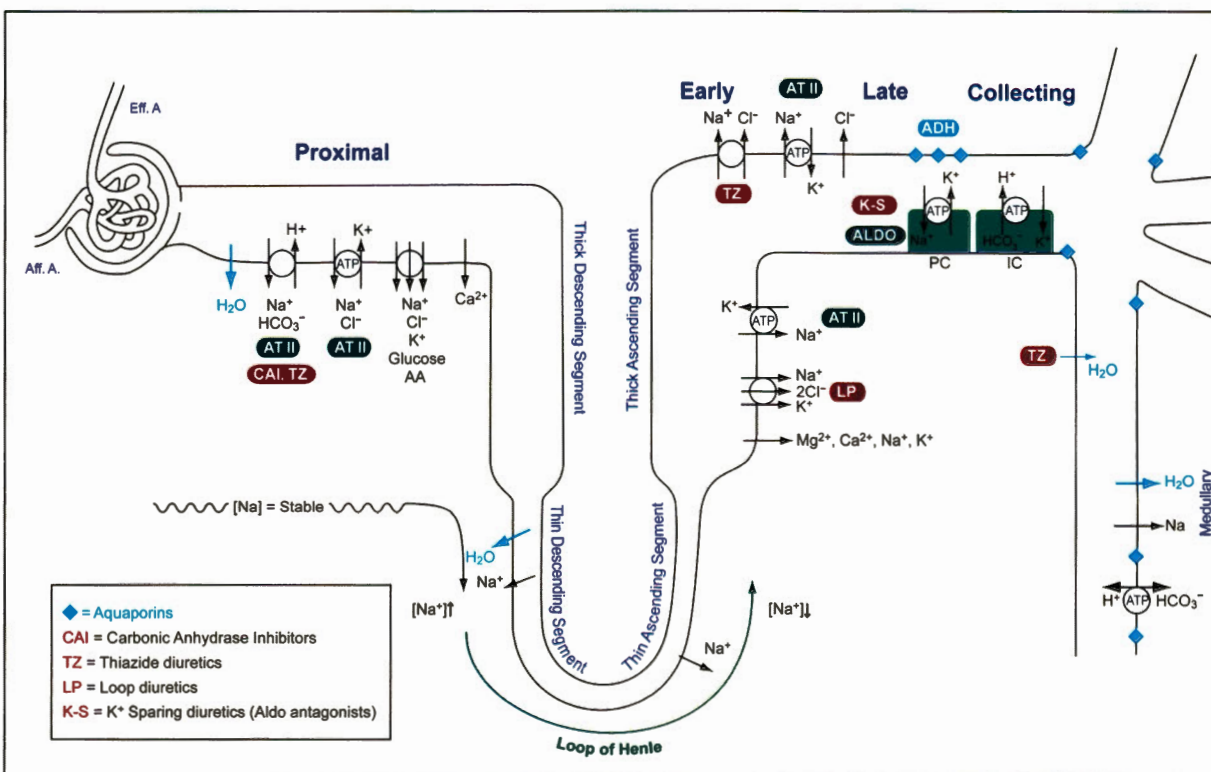


Figure 4-2: The Renal Tubule — Basic Physiology

water. Look at the specific cotransporter that is inhibited by loop diuretics. Notice that K^+ is also cotransported with that pump, so now it makes sense how patients taking loop diuretics also develop hypokalemia.

Loop diuretics also increase Ca^{2+} loss in the urine and have been used in the past to treat severe hypercalcemia. Normal saline was infused at a high rate (to replace the volume losses), and a loop diuretic was added. The saline expands the volume and delivers increased flow to the proximal tubule, which prevents paracellular Ca^{2+} reabsorption. The greatly increased Ca^{2+} load is then delivered to the distal tubule, overwhelming its ability to absorb Ca^{2+} , so calciuresis ensues.

In current clinical practice, saline is still given to volume-depleted patients with hypercalcemia; but **loop diuretics are considered questionable**—since we have the **bisphosphonates** that control calcium better and are associated with fewer electrolyte side effects.

By the time filtrate reaches the end of the thick ascending limb, it is fairly dilute because more solutes than water have been reabsorbed through the loop.

DISTAL TUBULE

The distal tubule is divided into **proximal** and **distal** (or “early” and “late”) segments because the actions of the sections differ.

The early distal tubule reabsorbs another 5% of remaining solutes with the following clinically relevant processes:

- Cotransport of Na^+ and Cl^- (into interstitium); inhibited by thiazide diuretics
- Counter-transport of Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by AT II
- Paracellular absorption of Cl^- (into interstitium)

Thiazide diuretics (chlorothiazide, hydrochlorothiazide, chlorthalidone) have to be secreted into the filtrate to be effective and, hence, are ineffective in patients with a low GFR. Remember that thiazides also slightly inhibit carbonic anhydrase in the proximal tubule. The effect of that is an increased delivery of Na^+ to the distal tubule and upregulation of the counter-transport of the Na/K ATPase. So, the more Na^+ that gets delivered to the distal pumps, the more K^+ that gets excreted. So, hypokalemia is also a feature of thiazide use.

Know that thiazides actually **encourage calcium reabsorption**, which is in contrast with the action of loop diuretics. This is important to remember, so you don't prescribe these drugs to patients with primary hyperparathyroidism or hypercalcemia of malignancy.

Clinically, the drug **chlorthalidone** is becoming a more popular diuretic than hydrochlorothiazide (HCTZ) because it is more potent and lasts 24 hours. Also, some major studies on hypertension (e.g., ALLHAT) used chlorthalidone, not HCTZ.

The **late distal** tubule and **cortical** tubule allow for further solute and water reabsorption, but, unlike the remainder of the tubules, the behavior of these segments is controlled by **aldosterone** and **ADH**.

Two important cell types in the **late distal** and **collecting** tubules reabsorb solutes:

- 1) **Principal cells:** Counter-transport Na^+ (into interstitium) and K^+ (into filtrate) via an ATPase active transport pump; stimulated by aldosterone and hyperkalemia and inhibited by potassium-sparing diuretics (amiloride, triamterene, spironolactone, eplerenone).
- 2) **Intercalated cells:** Secrete H^+ (into filtrate) via an ATPase active transport pump against a concentration gradient; for every H^+ secreted, one HCO_3^- is reabsorbed via the action of carbonic anhydrase. Thus, these cells are one of the major regulators of acid-base balance. Intercalated cells also reabsorb K (to a minor extent).

Water reabsorption in these segments is controlled by ADH. Through a complicated series of processes involving cyclic AMP and protein kinases, ADH calls forth an **aquaporin protein** (AQP-2) from the cytoplasm. Several AQP-2 molecules gather at the cell membrane and make a water channel, through which water is absorbed into the interstitium (cool, huh?). In the absence of ADH, these tubule segments are relatively impermeable to water. ADH receptors are inhibited by the ADH-receptor blockers—also termed “vasopressin receptor antagonists”: conivaptan (IV formulation only) and tolvaptan (oral).

Two diseases affect the distal and convoluted tubules:

- 1) Impairment of the H -ATPase active transport pump in the intercalated cells, which leads to inability to secrete acid (and reabsorb bicarbonate) = generation of **distal (Type 1 RTA) NAGMA**; urine pH is always > 5.3 .
- 2) Tubular aldosterone resistance = impairment of the Na/K ATPase counter-transporter $\rightarrow$ generation of **distal (Type 4) NAGMA**; **hyperkalemia** is present.

MEDULLARY COLLECTING DUCT

The remaining 10% of Na^+ and water are absorbed in the medullary collecting duct. Clinically relevant processes include the following:

- Presence of the H -ATPase, which allows for further acidification of the urine (and reabsorption of bicarb).
- Passive absorption of Na^+ .
- ADH-regulated reabsorption of water via aquaporins (proteins in cell membranes that regulate flow of water).
- Atrial natriuretic peptide (produced by the cardiac atrium in response to distention) inhibits Na^+ and water absorption in this segment (counteracting the effects of the renin-angiotensin-aldosterone cascade).

Quick Quiz

- Which 2 hormones exert their effects in the distal tubules?
- Stones are associated with which RTA?
- Multiple myeloma is associated with which RTA?
- What is the serum potassium level in distal, Type 4 RTA?
- Diabetic nephropathy causes which type RTA?

As discussed in the section on hyponatremia (page 4-8), new data suggest that thiazide diuretics increase permeability of the medullary collecting duct to water, but not via ADH. This phenomenon is not entirely understood.

RENAL TUBULAR ACIDOSIS

Overview

This section goes into more detail about Types 1, 2, and 4 RTA. RTAs are hyperchloremic NAGMAs. There is one proximal type (2) and two distal types (1 and 4).

Serum K⁺ level is **low to normal** in Types 1 and 2, and **high** in Type 4.

Type 1 RTA

Type 1, distal, RTA is a problem in the **H⁺-ATPase** of the intercalated cells in the distal and convoluted tubules that results in failure to acidify the urine. It is associated with hypokalemia (mechanism not completely understood) and hypercalciuria +/- nephrocalcinosis or stone formation. Urine is alkaline.

Most common causes:

- Genetic (presents in childhood)
- Autoimmune disease (Sjögren's, SLE, and rheumatoid arthritis)
- Hereditary hypercalciuria
- Drugs (amphotericin B, lithium)

Treatment is alkali therapy, K⁺ replacement, and addressing the cause.

Type 2 RTA

Type 2, proximal, RTA is a problem with proper functioning of cells in the proximal tubule (review on page 4-12). Remember that the proximal tubule is the area where most bicarbonate is reabsorbed by the kidney; therefore, bicarbonate wasting is the natural outcome of Type 2 RTA. So just think Type 2 RTA = bicarbonate wasting.

In Type 2 RTA, the proximal tubule is deficient in:

- Bicarbonate reabsorption
- Cotransport of Na⁺ with glucose, amino acids, Cl⁻, and K⁺

Most common causes of Type 2 RTA:

- Monoclonal gammopathies with buildup of light chains that damage the tubule cells
- Carbonic anhydrase inhibitors

Type 2 RTA may present as **Fanconi syndrome** (glucosuria, amino aciduria, and wasting of other solutes, including Mg, uric acid, and phosphorus). Urine is initially alkaline, then equilibrates and reacidifies.

Treatment is bicarbonate, potassium replacement, and vitamin D supplementation.

Type 4 RTA

Type 4, distal, RTA is a result of **hyporeninemic hypoaldosteronism** or **aldosterone resistance** in the principal cells of the distal and collecting tubules. The Na/K ATPase counter-transporter does not function. It is associated with hyperkalemia. The acidosis is mild.

The hyporeninemic hypoaldosteronism is usually a result of:

- Diabetic nephropathy
- Obstructive uropathy
- Chronic interstitial nephritis

Several common drugs can also suppress renin/aldosterone and lead to a hyperkalemic metabolic acidosis **similar** to Type 4 RTA:

- Spironolactone
- ACEIs, ARBs
- NSAIDs (exacerbates a concurrent hyporeninemic state)

Although it makes theoretical sense to treat this cause of Type 4 RTA with fludrocortisone (Florinef[®]; a synthetic adrenal corticosteroid with very potent mineralocorticoid effects), this therapy often leads to too much fluid retention.

Dietary restriction of sodium or bicarbonate administration may be sufficient treatment. Otherwise, give furosemide—a commonly used, effective treatment.

Review of RTAs

Clues to analyzing possible RTA:

All types are non-anion gap metabolic acidoses.

Type 1 RTA is caused by **hypercalciuria +/- nephrocalcinosis or stones**; high urine pH; definite **hypokalemia**.

Type 2 is caused by **bicarbonate wasting** and **Fanconi's**; urine pH and serum K are variable. Think **myeloma**.

Type 4 is associated with **aldosterone deficiency** or **resistance** and is marked by mild acidosis and **hyperkalemia**. Think causes of hyporeninemic hypoaldosteronism (interstitial disease, diabetes, NSAIDs, and ACE inhibitors).

Board exam questions concerning RTA may not even mention the terms “RTA.” Instead, questions may present patients with a history of nephrocalcinosis or diabetes or signs/symptoms suggestive of myeloma; then you may be asked to select the most likely serum and urine chemistry or the best treatment based on your interpretation of the given labs.

RTA Questions

After reviewing Table 4-6, answer the following questions that refer to Table 4-7.

Which chemistry profile, A thru E, in Table 4-7 is associated with the following clinical scenario:

- 1) DKA?
- 2) Patient with diabetes and chronic kidney disease?
- 3) Patient with myeloma?

- 4) Woman with nephrolithiasis?
- 5) Patient with heavy metal poisoning?
- 6) Patient with chronic diarrhea?

Here is one approach to analyzing a table like this:

First, peruse the values. Notice that all of the HCO_3^- values are low, and all of the Cl^- values are high (disproportionate to the Na^+). Think to yourself, “Oh yeah, hyperchloremic acidosis ... This may be one of those RTA problems.”

Next, calculate the AG for each, and label the ones with an increased AG “HAGMA.” (Note: Usually HAGMA has a normal Cl^- .)

Next, look for an alkaline urine ($\text{pH} > 6.0$), despite the low HCO_3^- . If so, check to see if the serum K^+ is also low to normal. If so, label it “proximal, Type 1 RTA—autoimmune, hypercalciuria.”

Next, look for a high serum K^+ , and label it “Type 4 RTA—hyporeninemic hypoaldo (diabetes, NSAIDs, ACEIs).”

Then, label the (probably) last one “Type 2 RTA—MM, Fanconi’s, heavy metals.”

Table 4-6: Renal Tubular Acidoses (RTAs)

	Type of Acidosis	Urine pH	Serum K^+	Misc.	Mechanism	Main Causes
Type 1 Distal	NAGMA	> 5.5	Low-nl	Stones	Decreased H^+ secretion in distal tubule	Autoimmune (SLE, Sjögren’s, RA) Hereditary hypercalciuria Drugs (amphotericin B, lithium)
Type 2 Proximal	NAGMA	< 5.5, although high initially	Low-nl	Fanconi’s	Decreased resorption of HCO_3^- in proximal tubule	MM Acetazolamide Amphotericin B Heavy metals Amyloidosis
Type 4 Distal	NAGMA	< 5.5	High	Diabetes	Decreased cation exchange in distal	Diabetic nephropathy Chronic interstitial nephritis NSAIDs ACEI Obstructive uropathy Spironolactone

Table 4-7: RTAs — Serum and Urine Chemistry

	Plasma				Urine		
	Na^+	K^+	Cl^-	HCO_3^-	pH	K^+	Na^+
Normal	135–145	3.5–5	95–105	22–30	variable	25–100	100–260
A	140	2.6	113	17	7.9	50	100
B	140	5.5	117	13	6	50	100
C	140	4.0	115	15	6	50	100
D	140	4.0	105	15	6	50	100
E	140	4.0	115	15	6	10	10

Quick Quiz

- Know [Table 4-6](#) and [Table 4-7](#)! Answer all of the questions.
- What K^+ derangement can be seen in Cushing syndrome?
- Addison disease causes what type of potassium derangement?
- Discuss the effects of NSAIDs on serum K^+ .
- How does the acid-base status affect K^+ levels?

NAGMA with a low urine sodium value is almost certainly diarrhea-induced volume contraction. Any HAGMA could be ethylene glycol, methanol, lactic/ketoacidosis, or salicylates. And what if you see a low anion gap? This means there is probably some artifactual lowering of the Na^+ . This occurs in hyperlipidemia and multiple myeloma (MM). We suspect that it would be in a MM patient with Type 2 RTA.

Correct answers are 1) D; 2) B; 3) C; 4) A; 5) C; 6) E.

MINERALS

POTASSIUM

Overview

Aldosterone

Basically, aldosterone can be considered the hormone that regulates potassium level. Recall from [page 4-14](#), K^+ secretion occurs in the late distal and collecting tubules via Na^+/K^+ active transport. Any situation that causes $aldo$ release (or mimics aldosterone) **lowers** the serum K^+ . These include:

- Increased renin as a result of decreased effective arterial blood volume:
 - Volume contraction
 - Decreased renal perfusion (HF, renovascular disease, NSAIDs)
- Increased renin as a result of inappropriate release:
 - Renin-secreting renal tumors
- Increased $aldo$ as a result of inappropriate release:
 - Bilateral adrenal hyperplasia
 - Aldo-secreting adrenal tumor ("Conn syndrome"; unusual)
- Increased excretion of hormone with $aldo$ -like effects:
 - Cushing syndrome

Conversely, any situation that inhibits $aldo$ release or $aldo$ action **increases** the serum K^+ :

- Potassium-sparing diuretics
- Dysfunctional kidneys that do not release renin (termed "hyporeninemic hypoaldosteronism";

chronic interstitial nephritis, diabetes, ACEIs, ARBs); exacerbated by NSAIDs

- Primary adrenal disease (Addison's), because it affects both the zona glomerulosa (site of $aldo$ production) and fasciculata (site of cortisol production)—but not secondary adrenal insufficiency because lack of ACTH affects **only** the zona fasciculata
- Heparins (Both unfractionated and low-molecular-weight are directly toxic to the zona glomerulosa.)

Know: NSAIDs can both increase and decrease renin, so they can make K^+ go up or down—but generally only if the patient has an existing problem that affects the kidneys. Basically, NSAIDs make hypo- and hyperreninemic states worse than they already are. See Other Drug-Induced Nephropathies on [page 4-43](#) for more explanation.

Cell Shifts

Cellular uptake also determines serum K^+ level:

- Alkalosis, beta-agonists, and insulin increase uptake → hypokalemia
- Acidosis and alpha-agonists decrease uptake → hyperkalemia

So this works both ways. Remember from the discussion on the proximal tubule ([page 4-12](#)) that hypokalemia can cause alkalosis, and **hyperkalemia** causes acidosis. So alkalosis causes hypokalemia and vice versa. And acidosis causes hyperkalemia and vice versa.

Other Factors Affecting K^+ Level

Potassium excretion by the kidney is stimulated by increased urine flow, the amount of Na^+ delivered to the distal tubule, aldosterone, the presence of non-reabsorbable anions in the tubules, and metabolic alkalosis. The following factors also affect serum K and are important to know:

- Increased cell turnover is associated with **hyperkalemia** (tumor lysis syndrome or acute leukemia).
- Trimethoprim in TMP/SMX interferes with K^+ secretion in the distal tubule, especially in patients with preexisting renal disease causing **hyperkalemia**.
- Type 1, distal, RTA is associated with **hyperkalemia** for unclear reasons.
- Type 2, proximal, RTA can be associated with **hyperkalemia** because of cotransport problems.
- Loop and thiazide diuretics block reabsorption of solutes and water. Thiazides increase distal delivery of solutes and up-regulate the Na^+/K^+ ATPase, causing **hypokalemia**.
- Cisplatin and penicillins are associated with renal K^+ wasting, causing **hypokalemia**.
- 3 genetic syndromes are associated with **hypokalemia**: Liddle's, Bartter's, and Gitelman's.

Summary

The following is the same information discussed previously, slightly reorganized and in list form.

Causes of Hypokalemia

Hypokalemia with metabolic alkalosis:

- Reduction in effective arterial blood volume
 - Volume contraction: vomiting, bleeding, or diuretics (thiazides and loops)
 - Renovascular disease: renal artery stenosis or fibromuscular dysplasia
 - Secondary hyperaldosteronism: severe HF, cirrhosis, nephrotic syndrome
 - NSAIDs (rare)
- Primary hyperaldosteronism
- Aldo-secreting tumor ("Conn syndrome")
- Renin-secreting tumor
- Cushing syndrome
- Liddle's, Bartter's, and Gitelman's (discussed on next page)

Hypokalemia with metabolic acidosis:

- Types 1 and 2 RTA
- Diarrhea

Hypokalemia associated with shifts into cells:

- Beta-agonists
- Insulin

Other causes of hypokalemia:

- Penicillins
- Cisplatin

Causes of Hyperkalemia

- Chronic interstitial nephritis
- Primary adrenal insufficiency ("Addison disease")
- Acidosis
- Drugs
 - Potassium-sparing diuretics
 - NSAIDs
 - ACEIs/ARBs
 - Heparins
 - TMP/SMX
 - Cyclosporine
 - Alpha-agonists

Hyperkalemia Manifestations

Most patients have no symptoms if the increase in the potassium has been chronic, even with a level near 7 mEq/L. Symptoms can manifest at lower serum levels when the increase is acute. Presentation can include significant weakness or paralysis, conduction abnormalities or arrhythmias. Typically, if a patient is experiencing weakness, he will also have ECG changes, although the opposite is not necessarily true.

Know the sequence of ECG changes that occur with progressive hyperkalemia:

Peaked T wave and short QT interval ...

→ progressive lengthening of PR and QRS intervals ...

→ loss of P wave + QRS widening into sine wave ...

→ ventricular fibrillation or cardiac standstill.

Hyperkalemia Treatment

Treatment is aimed at decreasing the serum concentration and stabilizing cardiac membranes. Problems usually occur when $K^+ = \sim 7$ mEq/L, but there is no absolute number that requires treatment. IV calcium is definitely and only given to patients with ECG changes.

Treatment of acute hyperkalemia with ECG changes:

- **IV calcium** gluconate (OK for peripheral injection) or IV calcium chloride (requires central access); use only if there is a wide QRS or absence of P waves. It is often not given with early ECG changes such as peaked T waves. IV calcium can cause digitalis toxicity.
- **Insulin with glucose** infusion (15 minutes for effect).
- **Sodium bicarbonate** injection or infusion, if acidosis is present (30 minutes for effect; minimal response in patients without acidosis).
- **Albuterol** nebulization (90 minutes for effect) or injection (30 minutes for effect), but be careful in patients with heart disease.
- **Loop diuretics** (in patients with intact renal function).
- **Dialysis**.

Sodium polystyrene sulfonate (SPS; Kayexalate®, Kionex®, Marlexate®) is a cation-exchange resin given orally or as an enema that exchanges Na^+ for K^+ across the gut wall and also induces an osmotic diarrhea full of potassium. SPS can be used to treat hyperkalemia, but it should **not** be used for treatment of severe hyperkalemia because it may take hours to work. Know that SPS in sorbitol (most common preparation) has been associated with colon necrosis, especially within a week after surgery and especially in patients with ileus.

Patients with severe chronic kidney disease or on dialysis should be treated as above, but they may also need immediate dialysis. SPS without sorbitol can be given if there is a delay in dialysis.

Treat $K^+ \geq 6.5$ without symptoms or ECG changes with insulin + glucose, beta-agonists, sodium bicarbonate (if acidosis), and SPS enema. $K^+ \leq 6.5$ can be treated with loop diuretics and dietary restriction.

Know that sodium bicarbonate infusions can cause edema and may precipitate cardiac decompensation.

Make sure you check the patient's medication list and discontinue all of the drugs that cause hyperkalemia.

Quick Quiz

- What are the ECG changes associated with hyperkalemia?
- What is special about the treatment of hyperkalemia in patients taking digoxin?
- What are 2 causes of NAGMA and hypokalemia?
- When hypokalemia is associated with HTN and alkalosis, what is the probable cause?
- What are the differences among Liddle's, Bartter's, and Gitelman's?

Hypokalemia Manifestations and Treatment

Overview

Severe hypokalemia may cause U waves, decreased deep tendon reflexes, and rhabdomyolysis. Serum K^+ does not decrease to below normal until there is a net loss of 200–300 mEq. The consequence of this is that large amounts of KCl are usually required for replacement.

Treat contributing factors such as volume depletion and/or metabolic alkalosis; also, do whatever tests are necessary to diagnose the cause (e.g., measure urine free cortisol to diagnose Cushing's; consider hyperaldosteronism). Replace potassium orally when possible. Poor response usually means the deficit is large, and the patient merely requires more potassium. Comorbid magnesium deficiency makes it impossible to replace potassium, so always check and replenish Mg stores.

Hyperaldosteronism

This entity is also discussed under Hypertension, page 4-22.

Primary hyperaldosteronism is caused by disease in the adrenal gland. Hyporeninemia, hypertension, and hypokalemia occur—as in other states of mineralocorticoid excess, such as Cushing syndrome. The adrenal disease is either bilateral adrenal hyperplasia or an aldosterone-secreting tumor in the zona glomerulosa (“Conn syndrome”).

Secondary hyperaldosteronism is caused by disease in the kidneys or a restriction of blood flow in the renal arteries. Hyperreninemia, hypertension, and, sometimes, hypokalemia occur. Decreased renal blood flow → increased renin → increased angiotensin II → increased aldosterone. The kidney disease is a renin-secreting tumor. The renovascular disease is either renal artery stenosis or fibromuscular dysplasia.

In both primary and secondary disease, aldosterone is increased, so the Na^+/K^+ ATPase in the distal and collecting tubules is up-regulated, resulting in increased reabsorption of sodium and increased secretion of potassium and hydrogen ions.

Hypokalemia without an obvious cause, in a patient with hypertension, should cause you to deliberately consider hyperaldosteronism. The evaluation of these patients is discussed under Secondary Hypertension, page 4-27. Hyperaldosteronism also is discussed in the Endocrinology section, Book 4.

Liddle Syndrome

Liddle syndrome is a rare genetic cause of hypertension and hypokalemic metabolic alkalosis in which there is primary Na^+ retention, mediated by an abnormal pump in the collecting tubules. Renin and aldosterone levels are decreased. Liddle's is treated with amiloride or triamterene.

Bartter and Gitelman Syndromes

Bartter's and Gitelman's usually are due to rare genetic or sporadic defects that cause abnormal solute transport in the **thick ascending** segment and the **early distal tubule**. Both are associated with severe sodium losses and eventual volume contraction with activation of the renin-angiotensin-aldosterone system. Renin and aldosterone levels are increased. Release of aldosterone is the mechanism for development of hypokalemia and alkalosis.

Bartter syndrome (4 types) is usually an autosomal recessive disorder, in which there is abnormal solute transport in the thick ascending segment that results in loss of Na , Cl , Ca , and Mg in the urine. Clinically, patients look like they are taking a loop diuretic. Bartter's type 4 has associated deafness. This syndrome usually presents in the neonatal period or early childhood due to salt-wasting and significant hypercalciuria, with stones or nephrocalcinosis.

Gitelman syndrome is caused by a defect in the Na^+/Cl^- cotransporter in the early distal tubule. This transporter is normally inhibited by thiazide diuretics; hence, patients with Gitelman's appear clinically as if they are taking a thiazide diuretic, except the patients have severe magnesium-wasting that is incompletely understood. Gitelman's is milder than Bartter's and usually presents later with symptoms of muscle weakness, cramps, and spasms due to hypomagnesemia.

Summarizing these 2 syndromes:

- Both cause hypokalemic metabolic alkalosis and salt-wasting without HTN.
- Bartter's: less common, childhood, disease of thick ascending limb, sometimes deafness, significant hypercalciuria.
- Gitelman's: more common, later presentation, disease of early distal tubule, significant hypomagnesemia, and hypocalciuria.

A Clinical Approach to Hypokalemia

It's hard to remember all of the conditions associated with low serum K^+ . The most helpful way to approach hypokalemia is to categorize patients according to whether or not they have a metabolic acid-base disorder, then whether or not they have hypertension.

Hypokalemia + NAGMA without HTN:

- K^+ loss is usually from diarrhea or Type 1 or 2 RTA.
- Clinical history and the UAG help differentiate.

Hypokalemia + metabolic alkalosis + HTN:

- Diuretics (most common) causing contraction alkalosis. The urine sodium is increased in spite of the volume contraction.
- Hyperaldosteronism (primary or secondary)
- Cushing syndrome
- Liddle syndrome
- Adrenal hydroxylase deficiencies

Hypokalemia + metabolic alkalosis without HTN:

- Bartter syndrome
- Gitelman syndrome

CALCIUM

Overview

Calcium is regulated by PTH and vitamin D metabolites, which affect rates of absorption in the kidneys and gut and rates of resorption of bone. Calcium derangements are discussed extensively in the Endocrinology section, Book 4.

The measured plasma calcium concentration is a total of free/ionized calcium (45%), calcium bound to albumin (40%), and calcium bound to other substances (15%). Ionized calcium is the state available for immediate use by the body and correlates with consequences of hyper- or hypocalcemia. Measure ionized calcium directly to get the most reliable assessment of a patient's calcium status.

Routinely, however, we measure the plasma calcium. If albumin decreases, the measured plasma calcium decreases, and you need to make a mathematical correction to estimate true calcium concentration (or measure an ionized calcium level to be precise). For each 1 g/dL decrease in albumin, increase the measured plasma calcium by 0.8 mg/dL. In pregnancy, calcium absorption and excretion is increased because the active form of vitamin D, $1,25-(OH)_2-D$, is $> 2\times$ normal.

Hypercalcemia

Hypercalcemia found incidentally in an asymptomatic patient is usually due to use of **thiazide** diuretics or to **1° hyperparathyroidism** (especially consider if there is a history of **neck irradiation**), but always consider multiple

myeloma, hypercalcemia of malignancy, and granulomatous disease.

Most patients with significant hypercalcemia are volume depleted and should receive normal saline replacement fluid. Calcitonin and bisphosphates are now standard of care for persistent hypercalcemia. Loop diuretics are no longer used to treat hypercalcemia.

Hypocalcemia

Hypocalcemia has several causes.

Most commonly:

- Vitamin D deficiency
- Chronic kidney disease
- Severe pancreatitis
- Rhabdomyolysis
- Hypermagnesemia (Always check magnesium level!)

Less commonly:

- Hungry bone syndrome following parathyroidectomy
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Citrate

Citrate is used as an anticoagulant in whole blood. It chelates calcium in the serum, causing hypocalcemia after massive whole blood transfusions. Know that the total plasma calcium concentration remains normal, and only the ionized fraction is reduced (but patients can have symptoms). Monitor patients who receive large amounts of blood or plasmapheresis by measuring their ionized calcium frequently.

Chronic kidney disease results in secondary hyperparathyroidism because of decreased renal conversion of 25-OH vitamin D to the active $1,25-(OH)_2-D$.

MAGNESIUM

Hypomagnesemia

Hypomagnesemia is **very common**. Causes are:

- GI disease, especially small bowel-associated malabsorption, chronic diarrhea, acute pancreatitis, and small bowel bypass procedures
- Kidney losses, especially tubular disease (acute tubular necrosis, Bartter's, Gitelman's) and drugs that affect the tubules (loop and thiazide diuretics, aminoglycosides, amphotericin B, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Miscellaneous causes, e.g., proton pump inhibitors (PPI, unknown mechanism, but patients can be so severely depleted that levels rise only after the PPI is discontinued), hungry bone syndrome (after parathyroidectomy), alcohol abuse, post-surgical state, and foscarnet use (due to chelation)
- Hypercalcemia

Quick Quiz

- What are the most common causes of asymptomatic hypercalcemia?
- What are the relationships between calcium and magnesium?
- Hypomagnesemia is associated with what other electrolyte abnormality?
- What is “refeeding hypophosphatemia”?

The relationship between **calcium** and **magnesium** is difficult to remember. Here’s the quick synopsis:

- Both increased and decreased magnesium can cause hypocalcemia.
- Increased calcium can cause hypomagnesemia.

Low magnesium also **causes** hypokalemia, so always check for low magnesium in patients presenting with hypocalcemia and/or hypokalemia because these deficiencies are not correctable until magnesium **stores** (not just the serum level) are replenished!

Clinical manifestations of hypomagnesemia most often occur with other electrolyte and/or mineral derangements such as hypokalemia or hypocalcemia. Muscle weakness, spasms, and tetany are the more common neuromuscular manifestations. ECG abnormalities precede cardiac manifestations (wide QRS and peaked T waves). Refractory cardiac arrhythmias are associated with depleted magnesium **stores** (even with a **normal** serum level).

Treatment can be oral in patients without symptoms, using a sustained release preparation—appreciating that the deficit is usually huge if the serum Mg level is low. Symptomatic patients should receive 50 mEq parenterally over 8–24 hours.

Hypermagnesemia

Hypermagnesemia, on the other hand, is **rare** and occurs from the use of:

- Mg-containing laxatives, antacids, or enemas in patients with renal failure (All are contraindicated in this group of patients.)
- MgSO₄ over-infusion during eclampsia treatment
- Less common, but noteworthy, causes: tumor lysis syndrome, milk-alkali syndrome, lithium overdose, Epsom salts ingestion (even as a gargle)

Symptoms begin when magnesium level is > 4–6 mEq/L: There is initial nausea, followed by sedation, muscle weakness, and a loss of deep tendon reflexes, progressing to paralysis (including heart and respiratory muscles).

Treatment: Treat acute symptoms with volume and calcium as an antagonist. Hemodialysis is necessary in renal failure. Don’t forget about hypocalcemia, which can develop as a result of increased magnesium concentrations.

PHOSPHATE

Hyperphosphatemia

Hyperphosphatemia—**acute** increase can be from:

- ATN (especially if due to rhabdo)
- IV solutions
- Rapid cell turnover (tumor lysis or acute leukemia)

Chronic increase of phosphate is seen in:

- Chronic kidney disease
- Hypoparathyroidism

See [page 4-44](#) for a discussion of the treatment of chronic hyperphosphatemia in CKD (the most common situation).

Hypophosphatemia

Hypophosphatemia—think alcoholism and alcoholic ketoacidosis. If severe ($\text{PO}_4 < 1 \text{ mg/dL}$), it may cause rhabdomyolysis (as can low K^+), cardiomyopathy, respiratory insufficiency with failure of diaphragm function, and nervous system problems, initially consisting of irritability and hyperventilation, then profound muscle weakness, then seizures, coma, and death.

Chronic malnutrition (as in alcoholics) results in increased catabolic release of phosphate, which then gets excreted by the kidneys, depleting total body stores. Even though an alcoholic may have a normal phosphate level on admission, he or she may become symptomatic with extreme muscle weakness a few days after a normal diet is established. This is because, as the glycogen level is returned to normal, the muscle cells become anabolic and take up phosphate, thereby reducing serum levels. This form of “**refeeding hypophosphatemia**” is a common clinical scenario.

Additionally, alcoholic patients with hepatic encephalopathy often have a respiratory alkalosis and may receive glucose solutions, both of which cause phosphate to enter cells, in turn causing severe hypophosphatemia, which may precipitate acute rhabdomyolysis.

Treatment of hypophosphatemia: Give supplemental phosphate to patients with DKA or those having alcohol withdrawal; it should be included in hyperalimentation fluid.

Patients with reduced renal function require less supplemental phosphate; phosphate supplementation may actually cause severe hyperphosphatemia.

Table 4-8: Volume Contraction

	Serum			Urine	
	Na ⁺	Cl ⁻	HCO ₃ ⁻	Cl ⁻	Calculated Osmo
Vomiting	low-nl	95	35	10	700
Diarrhea	low-nl	115	15	10	700
Thiazides	low-nl	95	35	100	700
Osmotic Diuresis	low-nl	nl	nl	100	300 (but high volume)

VOLUME CONTRACTION

Look for the following unique combination of factors in the answers to exam questions asking about volume contraction states (Table 4-8).

Vomiting (especially frequent, surreptitious vomiting) causes metabolic **alkalosis** and:

- Low serum Cl⁻ (losing stomach HCl in the emesis—makes sense)
- Hypokalemia from renal K⁺ wasting mediated by aldosterone

Diarrhea causes metabolic **acidosis** (NAGMA) and an appropriately high serum Cl⁻. (Bicarbonate is lost in the stool, and chloride is avidly reabsorbed to increase intravascular volume.)

Thiazide diuretics, like vomiting, cause a metabolic **alkalosis** with low serum Cl⁻ but, unlike vomiting, cause a high urinary Cl⁻ if the patient is actively taking the drug. Thiazides cause more Na⁺ to be delivered distally, where it is available for reabsorption and, therefore, stimulates H⁺ and K⁺ secretion. (See the discussion of thiazides under Normal Renal Physiology on page 4-12 and under Drugs for HTN on page 4-23.)

Volume contraction and diuretic use are associated with a concentrated urine. On the other hand, osmotic diuresis (mannitol, hyperglycemia) causes a high urine output with a normal urine osmolality, but increased solute and volume loss per day.

Remember: **Diabetes insipidus** (nephrogenic or neurogenic) may cause hypernatremia and volume contraction, but the patient can have a **normal** intravascular volume and sodium if water intake is sufficient—so it is only the patients who are unable to drink who become hypernatremic. This is discussed in the Endocrinology section, Book 4.

HYPERTENSION

NOTE

The following is adapted from the JNC 7 (7th report from the Joint National Committee on Prevention, Evaluation, and Treatment of Hypertension) published in 2003. This can be downloaded from the web:

<http://www.nhlbi.nih.gov/guidelines/hypertension/>

An update panel was convened in February 2008, and JNC 8 is expected to be released in 2012—although this release date has received continual extensions since 2009!

PRIMARY HTN

95% of all HTN is primary (i.e., essential, idiopathic). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) define the stages of HTN (the average of ≥ 2 readings taken from each of ≥ 2 visits after the initial screening:

Stage I: SBP 140–159 or DBP 90–99

Stage II: SBP ≥ 160 or DBP ≥ 100

In any of these stages, morbidity and mortality are higher for **men** than women, and higher for **African-Americans** than Caucasians. HTN itself is also more frequent in African-Americans than Caucasians. This **may** be due to a decreased Na⁺ excretion. HTN is well correlated with obesity in young persons. Of course, **primary** hypertension does have causes—they just have not yet been discovered.

If the diastolic blood pressure is < 85 , recheck it in 2–3 years. If 85–90, recheck it in 1 year. If 90–104, recheck within 2 months. If 105–114, work up within 2 weeks. If > 115 , work up immediately.

EVALUATION OF HTN

This is the standard evaluation for newly diagnosed hypertension. Initially, you look for major cardiovascular disease risk factors and **identifiable causes** of hypertension (Table 4-9).

History: Ask about history or symptoms of CHD (coronary heart disease), PVD (peripheral vascular disease), cerebrovascular disease, renal disease, DM, and lipid problems. Positive family history or symptoms of the same. Use of alcohol, smoking, street drugs, prescribed meds, diet history, psychosocial history.

Perform a full physical exam including **all** of the following:

General: height, weight, and waist size. Extremities: 2 BP checks (with verification in the other arm), other extremities for decreased pulses, bruits, and edema. Head: fundoscopic for hypertensive changes. Neck: bruits, enlarged thyroid. Chest: rales, wheezes. Full heart auscultation.

Quick Quiz

- Newly diagnosed hypertension in what age groups suggests that the cause might be secondary?
- What is the most common cause of secondary HTN?
- Review the 4 types of diuretics.
- Which diuretic is especially important to give to patients with systolic dysfunction and low ejection fraction?

Abd: Abnormal masses, bruits, abnormal pulsations.

Initial lab tests for all hypertensive patients: serum chemistry (Na^+ , K^+ , Cl^- , HCO_3^- , creatinine, fasting glucose), fasting lipid panel (T. chol, TG, LDL, HDL), serum Ca^{+2} , U/A, and a 12-lead ECG.

Indications for further evaluation for secondary causes of HTN include abnormal initial lab tests (hypercalcemia or hypokalemia), an abrupt onset, age < 30 years or > 55 years, malignant HTN, refractory HTN, or systolic-diastolic bruits in the epigastrium or lateralizing over a kidney. (Systolic bruits alone are **not** an indication.) Secondary HTN comprises only 5% of HTN cases. Renovascular HTN (renal artery stenosis and fibromuscular dysplasia) causing secondary hyperaldosteronism is the **most common** cause of secondary HTN. In the patient with hypokalemia and hypertension, consider whether the patient should be screened for hyperaldosteronism (discussed on [page 4-27](#)).

Other causes of secondary hypertension are Liddle syndrome, Cushing syndrome, chronic licorice ingestion, primary hyperaldosteronism, coarctation of the aorta, thyroid/parathyroid disease, chronic kidney disease, sleep apnea, drugs, and pheochromocytoma.

Table 4-9: Identifiable Causes of Hypertension

If you find this ...	Think this ...
Truncal obesity with purple striae	Cushing syndrome
Labile HTN	Pheochromocytoma
Continuous abdominal bruit	Renovascular HTN
Decreased BP in lower extremities or absent/delayed femoral pulses	Coarctation of the aorta
Abdominal or flank masses	Polycystic kidneys
Elevated creatinine or abnormal urinalysis	Renal parenchymal disease
Hypercalcemia	Hyperparathyroidism Granulomatous disease
Hypokalemia	Hyperaldosteronism

DRUGS FOR HTN

Overview

First, we discuss the specifics of the drugs used to treat HTN; then we discuss treatment of HTN.

Diuretics

Recall the 4 types of diuretics which were introduced along with Normal Renal Physiology starting on [page 4-12](#):

- 1) Carbonic anhydrase inhibitors
 - Inhibit Na^+/H^+ counter-transport in the proximal tubule
 - Complication: acidosis, hypokalemia
- 2) Loop diuretics
 - Inhibit the $\text{Na}^+/\text{2Cl}^-/\text{K}^+$ cotransporter in the thick ascending segment
 - Diminish the medullary osmotic gradient in the thin descending segment; effective at low GFRs but require higher dosing; contraindicated in sulfa allergy
 - Complications: hypokalemia, calciuresis, and ototoxicity
- 3) Thiazides
 - Inhibit the Na/Cl cotransporter in the early distal tubule
 - Slightly inhibit carbonic anhydrase in the proximal tubule
 - Increase water permeability of the medullary collecting duct
 - Ineffective at low GFRs; contraindicated in sulfa allergy
 - Complications: hypokalemia, hypercalcemia, metabolic alkalosis; may cause severe hyponatremia in elderly patients
- 4) K-sparing diuretics
 - Inhibit the aldosterone-controlled Na/K ATPase in the principal cells of the late distal and collecting tubules
 - Complications: hyperkalemia

Edematous patients with heart failure or chronic kidney disease should receive a loop diuretic. Patients with systolic dysfunction and low ejection fraction or problems with hypokalemia should receive spironolactone.

Diuretic-induced hypokalemia can be severe and is worrisome in patients with underlying cardiac problems and cirrhosis because of the potential for arrhythmias (especially if on digoxin) and hepatic coma. In hypertensive patients, hypokalemia can actually increase the blood pressure. Hypokalemia usually develops within the first 3 weeks of diuretic use, after which new homeostasis develops. Because higher doses only increase side effects, use the lowest diuretic dose needed to achieve the desired effect and monitor levels each time a dose

is changed. Know that 12.5 mg of HCTZ provides the greatest antihypertensive effect; 25 mg only causes more K wasting.

In HF and cirrhotic patients, it's best to keep the K > 4 with supplementation or K-sparing drugs.

ACE Inhibitors, ARBs, and Renin Inhibitors

Brief review: Renin is a protease released from the kidney in response to decreased blood pressure and effective arterial blood volume. Renin converts angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by means of proteolytic enzymes, including angiotensin-converting enzyme (ACE). Angiotensin II increases blood pressure by **direct vasoconstriction**, potentiation of the **sympathetic nervous system**, and stimulation of **aldosterone**.

ACE inhibitors (ACEIs: captopril, enalapril, benazepril, fosinopril, lisinopril, quinapril, moexipril, ramipril, perindopril, trandolapril) inhibit conversion of angiotensin I to II, causing a decrease in angiotensin II and aldosterone. Angiotensin receptor blockers (ARBs) act similarly at the angiotensin II receptor level. In the kidney, ACEIs/ARBs **dilate** the **efferent** artery (after the glomerulus) → decreased glomerular capillary pressure. This decreased glomerular pressure decreases progression of both **diabetic** and **hypertensive** nephropathies, and other types of chronic kidney disease.

ARBs (candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan,) are recommended in diabetics and patients with indications for ACE inhibitors but who are unable to tolerate them, usually due to cough.

Indications for ACEI/ARB

Absolute indications for ACEIs/ARBs: systolic dysfunction, history of STEMI or anterior NSTEMI, diabetes, chronic kidney disease (especially with proteinuria), and severe HTN with an ECG showing LVH.

Complications of ACEI/ARB

Complications of ACEI include an increase in serum K⁺ by ~ 0.5 mEq/L (possibly significant in patients with chronic kidney disease). Renal function can also decline. Recommendations are to stop the ACEI or ARB if the creatinine increases to > 30% over baseline, and/or the serum K is uncontrollable. The combination of heart failure + ACEI and sudden initiation of NSAIDs is particularly noteworthy for complications.

Up to 20% of patients have to stop an ACEI because of cough. Angioedema is a possible **fatal** side effect. ARBs have a lower incidence of angioedema and cough.

Know that the combination of an ACEI + ARB for treatment of HTN has been shown to cause increased adverse events (ONTARGET trial). Pick an ACEI **or** an ARB but do not combine them.

ACEIs/ARBs are absolutely contraindicated in pregnancy because they are **teratogenic**. Avoid in hyperkalemic patients and use with caution in bilateral renal artery stenosis, heart failure, polycystic kidney disease, and hypertensive nephrosclerosis because the ACEI-induced decreased GFR can precipitate acute kidney injury. ACEIs/ARBs have minimal CNS and sexual side effects.

Renin Inhibitor

The renin inhibitor, **aliskiren**, acts similarly to ACEIs/ARBs by blocking renin production. It has been approved since 2007 and has an average antihypertensive effect. Potential complications include diarrhea and angioedema. Renin inhibitors are also teratogenic.

In 2012, an interim analysis of international data on the use of aliskiren plus an ACEI or ARB in Type 2 diabetics showed an increased risk of stroke, hyperkalemia, low blood pressure, and renal insufficiency. This drug should not be combined with an ACEI or ARB.

Calcium Channel Blockers (CCBs)

These drugs are either **dihydropyridines** (amlodipine, clevidipine, felodipine, isradipine, nifedipine, and nisoldipine) or **non-dihydropyridines** that also depress cardiac contractility and reduce rate (verapamil and diltiazem). Both drug types are used to treat hypertension, angina, and arrhythmias.

Complications may include significant **edema** and **constipation** (especially with verapamil). Edema seems to form because the drugs vasodilate, and fluid leaks into the interstitium. Diuretics are ineffective at treating this edema. Edema is much less likely to occur if the dihydropyridine is given with an ACEI. Because of negative inotropic and chronotropic effects, do not give verapamil or diltiazem to patients also taking beta-blockers or who have heart blocks or severe heart failure.

Several studies have shown adverse associations (e.g., increased risk of death post-MI) with short-acting CCBs (but not long-acting ones). Dihydropyridines (but not verapamil or diltiazem) may cause proteinuria in patients with diabetes and chronic kidney disease. Even though many of the early CCB studies were poorly organized and analyzed, most experts do **not** recommend CCBs as first-line agents.

Beta-Blockers

Beta-blockers (acebutolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, pindolol, and propranolol) decrease cardiac output, sympathetic tone, and renin production. Each drug differs by its amount of lipid solubility, cardioselectivity, and sympathomimetic activity.

Quick Quiz

- ACEI and ARBs are absolutely contraindicated in what patients? Renin inhibitors?
- Why are beta-blockers not used as first-line drugs in patients older than 60 years?

Definite indications for beta-blockers:

- Post-MI
- Stable heart failure
- Atrial fibrillation (rate control)
- Angina

As monotherapy, beta-blockers are associated with increased risk of **stroke** and **heart disease** in patients older than **60** years, so they are not recommended **unless** one of the above indications exists.

Try to avoid beta-blockers in patients with reactive airway disease, frequent hypoglycemic episodes, hyperlipidemia, and PVD. Recall that nonselective beta-blockers (propranolol and labetalol) will increase the serum K^+ level slightly (~ 0.5 mEq/L), but this can be significant in patients with chronic kidney disease. Other complications include fatigue, erectile dysfunction, depression, and weight gain of up to 6 lbs.

Putting It all Together: Drug Studies

Know that several trials have demonstrated that the **degree of blood pressure lowering** is more important than the specific drug used to lower the BP, unless the patient has a specific comorbidity that would benefit from a specific drug.

The Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT) used monotherapy with chlorthalidone, amlodipine, lisinopril, or doxazosin to treat hypertension. The trial was stopped early because of an increased risk of heart failure in the amlodipine and lisinopril groups. Further analysis showed that patients in the chlorthalidone arm did better than the rest, primarily because that drug was more effective at lowering BP as a single agent than any of the other 3. Again, it's not about the specific drug chosen; it's about the degree to which the drug will decrease BP. (This is the study that convinced JNC 7 to recommend the thiazide diuretics as first-line agents for BP control.)

No specific drug type has been effectively demonstrated as "the best" for initial use, unless the patient has a specific comorbidity (e.g., diabetes with microalbuminuria, history of myocardial infarction, or history of HF; discussed below).

Bottom line: Use any drug, or combination thereof, with the fewest side effects, to get the **BP < 140/90** (or **130/80** for diabetes, chronic kidney disease, and coronary heart disease).

Acceptable first-line drugs for monotherapy include thiazide diuretics, ACEIs or ARBs, and calcium channel blockers. Beta-blockers should be used initially only if the patient has specific comorbidities (discussed below) because long-term data show increased adverse effects, especially in the elderly.

Some specifics regarding monotherapy for HTN:

- Monotherapy with a thiazide, ACEI/ARB, or long-acting calcium channel blocker is fine for patients with **mild** hypertension.
- African-Americans do better with a thiazide or a long-acting calcium channel blocker.
- Young patients do best with an ACEI. As patients age, they often require additional drugs.

Patients who are not controlled with monotherapy usually have a better response with the addition of a low-dose 2nd drug, rather than an increase in dose of the 1st drug.

Two drugs as initial treatment are recommended in patients with BP > 160/100. Which combinations are best is controversial, but an **ACEI** + long-acting **calcium channel blocker** is the most popular initial regimen based on clinical trials.

TREATMENT OF ESSENTIAL HTN

The JNC 7 Guidelines

According to JNC 7, appropriate antihypertensive treatment decreases all hypertensive complications (stroke, LVH, HF, renal failure), **except** atherosclerotic heart disease.

General lifestyle guidelines for preventing and controlling hypertension:

- Stop smoking.
- Lose weight.
- Get regular aerobic activity.
- Moderate alcohol and Na^+ intake.
- Maintain sufficient intake of K^+ , magnesium, and calcium.
- Reduce intake of saturated fat and cholesterol.

JNC 7 states that if lifestyle changes are insufficient, initial **drug therapy** of uncomplicated Stage 1 essential HTN should begin with the lowest doses of a **thiazide** diuretic.

For Stage 2 hypertension, give a diuretic combined with a second agent. As discussed above, however, several studies (since publication of JNC 7) have shown that outcomes are based on the total reduction in blood pressure—not on the specific drugs used to make the reduction (unless comorbidities; discussed next).

No one drug is specifically recommended over others for mono- or dual therapy, except in patients with the following **comorbidities** (which you should definitely know):

- **Angina pectoris:** **Beta-blockers** and long-acting **calcium antagonists** are recommended. (Avoid short-acting calcium antagonists.)
- **Post-MI:** **Beta-blockers** reduce recurrent MI. **ACE inhibitors** prevent subsequent heart failure and reduce other endpoints.
- **Left ventricular hypertrophy (LVH)** is a major risk factor for CV events (heart failure, MI, arrhythmias, sudden death, and stroke)—whether diagnosed by ECG or echo, and regression of LVH is associated with reduced risk. Drugs that reduce LVH include **ACEIs/ARBs/renin inhibitors**, certain **CCBs**, and some **alpha-blockers** (but alpha-blockers are not recommended as monotherapy for HTN). Beta-blockers, diuretics, and vasodilators such as hydralazine do not seem to affect LVH.
- **Systolic dysfunction:** **ACEIs/ARBs** alone or with diuretics, beta-blockers, aldosterone antagonists.
- **Proteinuria** > 1 g/24 hr: Control BP to 130/85. Use **ACEIs** or **ARBs**.
- **Diabetes:** **ACEIs** or **ARBs**, **alpha-blockers**, **CCBs**, and **diuretics** are preferred.
- **Diabetic nephropathy:** Use **ACEIs** or **ARBs** as initial therapy.
- **Asthma:** Avoid beta-blockers and alpha-beta-blockers. **ACEIs** or **ARBs** are safe in most.
- **Gout:** Avoid diuretics because they may induce or worsen hyperuricemia.
- **Hypercalcemia:** Avoid thiazide diuretics because they increase calcium reabsorption in the tubules.
- **Stroke:** After an acute embolic/thrombotic stroke in the hypertensive patient, pay careful attention to recommendations on reducing blood pressure. Rapid reduction of BP can extend infarction because the

sclerotic vessels in the brain need a higher perfusion pressure to function normally. See the Neurology section, Book 5, for detailed discussion on acute and chronic treatment of stroke.

The Elderly

Hypertension is common in the elderly—a 60–80% incidence! Elderly persons generally have **isolated systolic** hypertension (SBP > 160); but diastolic HTN also occurs, and **you should treat both**. The data now **strongly support** treating isolated systolic hypertension, even in patients older than 80 years. The degree of **systolic** hypertension and the increase in pulse pressure are directly correlated with poor outcomes.

Treatment of HTN in the elderly begins with lifestyle changes—especially decreasing weight and dietary salt. If drugs are needed, be sure to exclude the presence of baseline orthostatic hypotension before choosing an agent. Also, start with 1/2 the normal lowest dose.

The best antihypertensive drugs in elderly are low-dose thiazides (hydrochlorothiazide or chlorthalidone), long-acting dihydropyridine CCBs, and ACEIs or ARBs.

In patients older than 80 years, the target blood pressure has been modified to SBP 140–145; avoid blood pressures < 130/65.

HYPERTENSIVE CRISES

There are 2 main clinical expressions of end-organ damage caused by severe HTN:

- Malignant HTN, which is severe HTN with papilledema, retinal hemorrhages (**Image 4-1**), or exudates that may also be associated with nephrosclerosis (which presents as acute kidney injury +/- active urine sediment).
- Hypertensive encephalopathy, which is severe HTN with signs of cerebral edema (which presents as headache, nausea/vomiting, confusion, coma, and/or seizures). (This condition must be differentiated from acute stroke with imaging.)

Treatment goal is rapid decrease of the diastolic BP to 100–105 mmHg within 2–6 hours, while minimizing the drop so as not to reduce the presenting BP by > 25%. Generally, IV agents are used (e.g., nitroprusside, nicardipine, labetalol) because oral drugs reduce the BP in an uncontrollable way. If the patient is **asymptomatic** or there are no parenteral drugs available, you can use **oral** drugs. Keep in mind that **too rapid** of a drop in BP may cause an ischemic stroke or MI. Drugs used are loop diuretics, beta-blockers, alpha-blockers, and CCBs. Oral agents are not the standard of care, however, if the above parenteral options are available.

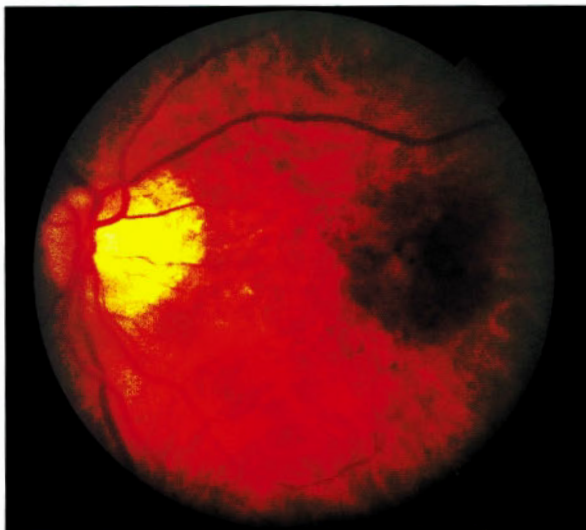


Image 4-1: Retinal hemorrhage

Michael Abbey Photo Researchers, Inc.

Quick Quiz

- What antihypertensives should be used to treat post-MI patients?
- What is the hypertensive treatment goal for patients with proteinuria?
- What are the best drugs to use to treat hypertension in elderly patients?
- What is the goal for blood pressure reduction in patients who present with hypertensive crisis?
- What is the main cause of renovascular hypertension in men > 50 years old?
- What is the main cause of renovascular hypertension in women < 40 years old?
- What does the combination of a continuous abdominal bruit and a low K⁺ imply in a hypertensive patient?

SECONDARY HYPERTENSION

Renovascular HTN

Renovascular disease causing secondary hyperaldosteronism is the **most common** cause of secondary HTN.

The 2 main causes of renovascular hypertension:

- 1) Atherosclerotic renal artery stenosis (often **bilateral**, mainly affecting **men > 50 years old**, especially diabetics)
- 2) Fibromuscular dysplasia (also often **bilateral**, mainly affecting **women < 40 years old**)

Less common causes of renovascular HTN include scleroderma and various vasculitides (e.g., Takayasu's).

So consider renovascular HTN when you see moderate-to-severe HTN with onset in patients < 30 years of age (fibromuscular), onset of HTN in patients > 55 years of age (atherosclerotic), HTN + unexplained hypokalemia, and accelerated HTN.

Diagnosis: Renovascular HTN may cause a continuous renal bruit, **not** an isolated systolic bruit. Know that the combination of a continuous abdominal bruit and hypokalemia in a hypertensive patient is strongly suggestive of renovascular HTN—especially if they have other risk factors (> 55 years old, diabetic).

Screen patients with possible secondary hypertension caused by renovascular disease with noninvasive tests first—if their serum **potassium** levels are **normal**. Choices are helical CT, MR angiography, and duplex Doppler ultrasound of the renal arteries, with the first two being the most sensitive. Work up only those patients who are moderate-to-high risk for disease and who are surgical candidates. Definitely **do not screen** elderly patients with mild hypertension and a normal serum potassium.

When screening for renovascular disease in patients with normal serum K, definitely **do not** use the following tests: captopril renal scintigraphy, selective renal vein renin measurements, isolated plasma renin activity, or an IV pyelogram.

For patients with possible secondary hypertension and hypokalemia, proper screening includes an evaluation for disease in the adrenal gland, termed “primary hyperaldosteronism.” In these patients, start with the **PAC:PRA** test (discussed next).

So, just to review. In patients with possible secondary hypertension, if the serum K is:

- Normal: Go straight to evaluation of the renal vasculature with helical CT, MRI, or Doppler. Do not screen patients who are not surgical candidates (e.g., elderly with mild HTN).
- Low: Screen for primary hyperaldosteronism using the serum PAC:PRA (discussed below).

Arteriography is the **gold standard** for diagnosis of renovascular HTN, but the procedure is invasive, with potential for serious complications. Use it to confirm positive noninvasive screening tests. Fibromuscular dysplasia shows up as a “string of beads” with multiple, little aneurysmal dilatations. An atherosclerotic lesion is usually a single, unilateral, proximal stenosis with distal dilation. Not all lesions found on angiogram are functionally significant, so it is very important to consider a patient's likelihood of true disease prior to ordering the test.

Treatment: Fibromuscular dysplasia can frequently be treated with angioplasty/stenting, but treatment of atherosclerotic renal artery disease is controversial and does not always improve hypertension.

Primary Hyperaldosteronism

Aldosterone is secreted by the adrenal zona glomerulosa in response to renin stimulation → Na⁺ uptake/K⁺ secretion in the principal cells of the late distal tubule. Suspect hyperaldosteronism (primary or secondary) in a person not on diuretics who has hypokalemia of unknown etiology. The person may or may not be hypertensive. There are 2 main causes of the primary form: adrenal adenomas (70%; sometimes called “Conn syndrome”) and idiopathic bilateral adrenal hyperplasia (~ 25%). Adrenal carcinoma is a rare cause.

Screening and diagnosis: Screen with a plasma aldosterone concentration (PAC) and plasma renin activity (PRA). The paired hormones can be analyzed as a ratio (PAC:PRA).

In primary hyperaldo (disease in the adrenal), the PAC is increased, but the PRA is suppressed such that the ratio is usually > 20. If this screening suggests primary hyperaldo, assess whether you can suppress aldosterone after salt and fluid loading. Give 2 liters of normal saline IV over 3–4 hours while the patient is recumbent, then

check the aldo level. Alternatively, you can give an oral salt load over 3 days and check the aldo level. In either situation, if aldosterone is not suppressed, the patient has primary hyperaldosteronism.

Also, if the patient is already on an ACEI or ARB, draw renin and aldosterone levels to see if aldosterone is suppressed; if not, this also supports the diagnosis of 1° hyperaldosteronism.

Once you know you're dealing with aldosterone excess, do a CT scan of the adrenals to characterize the gland: Is there hypertrophy or an adenoma?

Initial treatment of primary hyperaldosteronism:

- Salt and water restriction
- K⁺-sparing diuretics:
 - Spironolactone
 - Triamterene
 - Amiloride
- +/- Thiazide diuretic

Unilateral adrenal adenomas are surgically removed with excellent results, whereas patients with bilateral hyperplasia are managed with diuretics alone because bilateral adrenalectomy resolves the HTN in only 33% of these patients.

Cushing Syndrome

Cushing syndrome is covered in the Endocrinology section, Book 4.

Pheochromocytoma

Pheochromocytomas are **very rare** tumors arising from **chromaffin** tissue. 90% occur in the adrenal **medulla**. The rest are abdominal or thoracic. 10% are bilateral; 10% are **malignant**; and 10% are **familial**. Although commonly thought of with paroxysmal symptoms, 1/2 to 2/3 of patients have **sustained** HTN. Especially suspect this if the HTN is **refractory** to treatment. It is associated with multiple endocrine neoplasia (MEN) IIA and IIB.

Diagnosis: Screen with 24-hour urine for fractionated metanephrines and catecholamines in patients with low pretest probability.

In higher-risk patients (family history of pheo, MEN II, or neurofibromatosis [von Hippel-Lindau disease]), screen with fractionated metanephrines on a random plasma sample. This test is the least specific and may be false positive in patients with less risk of disease. Screening is somewhat controversial, but all agree with a 24-hour urine for fractionated metanephrines and catecholamines. If the biochemical tests suggest a pheo, get a CT or MRI of the abdomen and pelvis using contrast. If imaging doesn't show a tumor, and you still suspect one given the biochemical tests and history, consider metaiodobenzylguanidine scintigraphy. Metaiodobenzylguanidine is a norepinephrine analog that concentrates in an adrenal pheo. Tricyclic drugs

interfere with the 24-hour urine tests, so wean your patients before testing. More on pheochromocytomas in the Endocrinology section, Book 4.

Pregnancy and HTN

In normal pregnancy, the blood pressure is reduced due to an increase in systemic vascular resistance. Therefore, the BP should always be < 120/80 in pregnancy. There are 4 categories of HTN in pregnancy:

- 1) **Chronic HTN**: preexisting HTN or HTN before 20th week of gestation.
- 2) **Preeclampsia**: HTN + proteinuria **after 20th week** of gestation in woman with no history of HTN.
- 3) **Gestational HTN** occurs **after 20th week** and has **no** proteinuria in woman with no history of HTN.
- 4) **Preeclampsia that complicates chronic HTN**: worsening HTN + proteinuria after 20th week of gestation in a woman with history of controlled, chronic HTN.

The JNC 7 stages of HTN do not apply in pregnancy. HTN in pregnancy is defined as:

- mild if BP is 140–159/90–109 or
- severe if BP ≥ 160/110.

Eclampsia is defined as grand mal seizures in a woman with preeclampsia or gestational HTN. Preeclampsia (or pregnancy-induced hypertension; PIH) more commonly occurs in primigravidas, usually in the 3rd trimester, and resolves after delivery.

Note: The defining feature of preeclampsia is proteinuria, not symptoms. Thus, we have 2 additional categories of preeclampsia: symptomatic and asymptomatic (both have proteinuria). Symptoms of preeclampsia can be mild (headache, vision changes) or severe (seizures [eclampsia], low platelets, stroke or intracerebral hemorrhage, pulmonary edema, hepatic and/or renal failure, and placental abruption). HELLP syndrome is preeclampsia with **elevated** liver enzymes, **low** platelets, and **microangiopathic hemolytic anemia**.

Treat all hypertension occurring during pregnancy (regardless of category) to prevent stroke. Note that treatment of hypertension does not affect the outcome of any preeclampsia (weird ... but true).

Know that pregnant women with hypertension are at risk for adverse fetal outcomes if blood pressure is driven too low. This is one patient group in whom we actually have higher BP goals, not lower! Each 10 mmHg reduction in SBP is associated with a reduction in fetal birthweight.

For women with preeclampsia, recommendations are to start treatment 1) if symptoms are present or 2) in asymptomatic women when SBP ≥ 150 or DBP ≥ 95 (although these specific numbers are controversial), with a target BP goal of < 130–150/80–100. Bedrest is still recommended for asymptomatic or mild preeclampsia (especially if before 34-weeks gestation), although there are no clinical trials to suggest it affects

Quick Quiz

- How do you confirm the diagnosis of primary hyperaldosteronism?
- How do you screen for pheochromocytoma?
- What are the 4 categories of hypertension in pregnancy?
- What is the definition of “eclampsia”?
- What is the defining feature of preeclampsia?
- What is the definition of “oliguria”?
- What is the underlying cause of prerenal kidney injury?

outcome. For severe, symptomatic preeclampsia, definitive treatment is delivery. Ultimately, care providers walk a fine line between delivering a baby too early to relieve preeclampsia and allowing for longer gestational development.

Women who are pregnant and have chronic HTN that is controlled (BP < 120/80) are taken off BP meds—but get frequent BP and symptom monitoring. (That’s right! This is the one instance where antihypertensives are actually **removed**!) Meds are reinstituted for the same BP as mentioned above for preeclampsia (SBP ≥ 150 or DBP ≥ 95) with a target of < 130–150/80–100.

Any pregnancy complicated by malignant HTN (see [page 4-26](#)) or severe, symptomatic preeclampsia is treated with parenteral antihypertensives—labetalol is the preferred drug. Hydralazine and CCBs are also sometimes used, but there is less data for these drugs.

Know that the following antihypertensives are contraindicated: ACEIs/ARBs, renin inhibitors, and nitroprusside (cyanide poisoning in the baby).

Oral agents used to treat chronic, asymptomatic preeclampsia, gestational hypertension, and chronic hypertension in pregnancy include **labetalol** (other beta-blockers have less desirable effects, so labetalol is preferred), **methyldopa**, extended-release **nifedipine**, and **thiazide** diuretics (but watch for signs/symptoms of volume contraction).

Be aware that eclampsia can definitely occur postpartum, although rarely. A woman who presents hypertensive with generalized seizures within 12 weeks after delivery should be considered eclamptic.

Other Causes

Other important 2° causes of HTN that must be excluded include birth control pills and coarctation of the aorta. Treatment of obesity, decreasing alcohol intake to ≤ 2 drinks per day, and addressing a deficiency in **calcium** or **potassium** in the diet may normalize blood pressure in some patients with mild HTN.

ACUTE KIDNEY INJURY

OVERVIEW

The general term “acute renal failure” has been replaced with “acute kidney injury” (AKI) to better represent a wide spectrum of potential kidney damage—not just failure.

Small changes in serum creatinine can be associated with significant adverse clinical consequences. AKI should be evaluated by excluding prerenal and postrenal causes while evaluating for intrinsic kidney disease.

AKI can be either non-oliguric, oliguric, or anuric. **Oliguria** is < 400 mL/d urine volume. **Anuria** is < 50 mL/d.

Refer to [Table 4-10](#) on [page 4-30](#) while reading about acute kidney injury.

Prerenal AKI is caused by underperfusion, either from true loss of volume or decreased effective arterial blood volume.

Postrenal AKI is caused by obstruction within the urinary system.

Intrinsic AKI is caused by a problem with the glomeruli, tubules, or interstitium.

In all patients with AKI, specifically focus on drug exposures and volume status as part of the history. Initiate the diagnostic workup with orthostatic vital signs, a U/A, fractional excretion of sodium, and renal ultrasound.

PRERENAL AKI

Prerenal AKI is always due to a real or “effective” decrease in renal **blood flow**:

- Severe intravascular volume loss from volume depletion, blood loss, hypotension, or diuretics
- Renal artery stenosis or fibromuscular dysplasia causing reduced blood volume to the kidneys
- Renal atherosclerotic emboli (can present as prerenal or intrinsic renal AKI)
- Systolic dysfunction
- Drugs that cause vasoconstriction of the afferent and/or efferent arterioles:
 - NSAIDs (afferent)
 - ACEIs/ARBs (mainly efferent)
 - Post-transplant immunosuppression drugs (afferent)
- Hepatorenal syndrome

If the patient has no indication of hypovolemia on physical exam, consider the other causes listed above—all are associated with reduced glomerular pressure. Additional clues as to the specific prerenal cause of AKI include:

- NSAIDs in the history: As we discuss on [page 4-43](#) (drug-induced nephropathies), NSAIDs cause **constriction** of the **afferent** arteriole and a decrease in

Table 4-10: Acute Kidney Injury Labs and Clues

Category	Causes	FE _{Na}	U _{Osm}	Urine Na ⁺	Urine Sediment	Suspect in Patient with ...
Prerenal	Volume depletion Decreased EABV* NSAIDs ACEI	< 1%	> 400 mOsm/L	< 20	Normal Granular casts Hyaline casts	Bleeding CHF Cirrhosis Nephrotic syndrome
Intrinsic renal	Diseases of the glomeruli, tubules, or interstitium	ATN > 2% GN < 1%	300–350 mOsm/L	> 20	Red cell casts and/or protein (GN) Dirty brown casts (ATN) Eos (AIN)	Infections SLE Vasculitis Drugs Heroin Myeloma Diabetes HTN
Postrenal	Obstruction	Normal	Normal	Normal	Hematuria	Elderly males Colicky pain

*EABV = effective arterial blood volume

GFR, especially in patients who have comorbidities with preexisting, decreased effective arterial blood volume, such as systolic dysfunction or cirrhosis.

- Baseline **hypertension** and **hypokalemia** or recent prescription of an ACEI or ARB: Consider renal artery stenosis or fibromuscular dysplasia.

About cholesterol atheroemboli ...

Remember that atheroemboli can have a variable presentation. Emboli may occur after vascular surgery (especially of the aorta) or arterial catheterization in the atherosclerotic patient.

There can be showers of cholesterol emboli that settle systemically in the extremities and in the kidneys, causing a “**stepwise progression**” of renal failure, abdominal pain, livedo reticularis, and blue toes. Hollenhorst plaques may occur. These are cholesterol emboli in the retinal arterioles that appear as orange-white dots interrupting the circulation. Labs often show eosinophilia +/- eosinophiluria, and hypocomplementemia, or may show proteinuria and/or hematuria (which would represent more of an intrinsic AKI manifestation). If diagnosis is in doubt, a skin biopsy of one of the systemic lesions can show a cholesterol embolus. Treatment of AKI due to cholesterol emboli is **supportive only**. Do **not** anticoagulate.

Note that **renal** atheroemboli can be considered **prerenal** (because it blocks renal blood flow) or **intrinsic** renal (because it usually affects small intrarenal vessels). We discuss the topic here because, often, the labs look “prerenal.”

Evidence of portal hypertension (ascites, esophageal varices, splenomegaly, leucopenia, thrombocytopenia, anemia) and jaundice: Think **hepatorenal** syndrome.

AKI due to hepatorenal syndrome is a severe vasomotor disturbance caused by splanchnic dilation. It is a diagnosis of exclusion with criteria that include evidence of portal HTN + rising creatinine over time, normal U/A, normal renal U/S, low FE_{Na}, cessation of toxic drugs, and no improvement with volume resuscitation. Therapy with midodrine and octreotide is aimed at stabilizing patients until they receive liver transplant.

So after reading the above topics, you know that interventional radiologic catheterization may cause 2 different renal problems:

- 1) Immediate contrast ATN (improves and has no skin findings)
- 2) Cholesterol atheroemboli (livedo reticularis, eosinophilia, obvious systemic emboli, kidney injury)

Prerenal AKI: Labs

BUN:Cr ratio is usually increased.

Urine is very concentrated with osmolality often > 700.

Urine Na⁺ is < 20, indicating normal tubular function (and avid reabsorption of Na⁺ to increase glomerular pressure).

Urine sediment is usually normal but can show granular or hyaline casts.

FE_{Na} is < 1% in both prerenal AKI and acute glomerulonephritis (GN; see equation 3 on page 4-2). To differentiate, AKI with a FE_{Na} < 1% and a normal urine sediment +/- few granular or hyaline casts = **prerenal** azotemia. Red cells, red cell casts, and protein indicate GN.

POSTRENAL AKI

Postrenal AKI can result from either **external compression** of the urinary tract, or intraluminal/intratubular **obstruction**.

Quick Quiz

- Again, what diagnoses do you consider in a patient with hypertension and hypokalemia?
- What is a Hollenhorst plaque?
- What are some manifestations of cholesterol emboli?
- What are the lab findings in prerenal azotemia?
- With postrenal AKI, how does the amount of urine produced relate to the degree of obstruction?
- ATN is usually due to what 2 causes? Name the major nephrotoxins.

Intratubular obstruction can be caused by uric acid precipitation, oxalate depositions, hypercalcemia with intrarenal deposits (remember Type 1, distal, RTA!), multiple myeloma, and certain drugs, especially **methotrexate**, **indinavir**, **acyclovir**, **ganciclovir**, and **sulfa antibiotics**, which can crystallize in the urine.

Having 2 kidneys protects from unilateral obstruction because the 2nd kidney simply takes over total function. Usually, the obstruction is bilateral if the patient develops AKI and has normal kidneys—or the patient has obstruction in a solitary kidney (other kidney removed).

Prostatic hypertrophy and stones are the usual causes of postrenal AKI in internal medicine patients. Recall that Type 1 (distal) RTA is associated with calcium stone formation. Stones are specifically discussed on [page 4-49](#). Urethral stenosis and cancer less commonly cause outlet obstruction.

Know that the amount of urine produced does not really give you an indication about the degree of obstruction. Obstructed patients can even have increased urine output because of chronic damage to the tubules that impairs their ability to reabsorb water and solutes. Anuria, however, almost never occurs with obstruction unless it is complete (usually associated with shock).

Postrenal AKI: Labs

Creatinine is usually normal in partial obstruction and elevated in bilateral obstruction.

U/A is usually “bland” (no abnormalities). **Papillary necrosis** (the papillae are just before the renal pelvis) occurs in pyogenic kidneys with postrenal obstruction, chronic analgesic abuse, and sickle cell disease. U/A shows sterile pyuria with WBC casts.

Diagnose obstruction with renal U/S or CT scan (if you suspect stones).

INTRINSIC RENAL AKI

The 3 main categories will be discussed next as major headings:

- 1) Acute tubular necrosis (ATN)—discussed first because, in association with a prerenal state, it is the most common cause of intrinsic renal AKI
- 2) Interstitial nephritis
- 3) Glomerular disorders

ACUTE TUBULAR NECROSIS

OVERVIEW

Acute tubular necrosis (ATN) is a more common cause of AKI than glomerulonephritis or interstitial disease. ATN causes about 1/2 of the cases of AKI in the hospital. When considering that prerenal causes lead to ATN in the majority of cases, the combination of the 2 causes 75% of the cases of AKI.

CAUSES OF ATN

ATN is caused by **transient ischemia** or a **nephrotoxin**. Ischemia may be due to shock or any other condition that causes an abrupt decrease in renal perfusion.

Nephrotoxins include:

- Myoglobin (from rhabdomyolysis, discussed below)
- Hemoglobin (from chronic hemolytic states)
- Heavy metals
- Contrast dye
- Drugs (aminoglycosides, amphotericin B, foscarnet, cidofovir, pentamidine, cisplatin, IVIG, and many others)

Notes on drug-induced ATN:

- Amphotericin B is especially likely to cause ATN at > 3 gm total dose. Amphotericin B has a direct nephrotoxic effect and can cause a Type 1 or 2 RTA.
- Aminoglycosides (AG) cause **proximal** tubule damage, resulting in a non-oliguric ATN and hypomagnesemia. Often the ATN presents **5–7** days from the start of treatment. Once-daily AG dosing is less nephrotoxic than multi-daily doses. Gentamicin is the most toxic AG.
- Cisplatin is a common chemotherapeutic cause of ATN. It also causes a magnesuria and hypomagnesemia.

Tubular dysfunction is the hallmark of disease. Renal epithelium necrotizes, and the tubules essentially fill up with debris so they no longer function. Think back to the drawing of the tubules and consider what the tubules do (reabsorb water and solutes; secrete H⁺ and K⁺)—then you can predict how ATN presents.

LABS IN ATN

BUN:Cr ratio is 10–15:1.

Tubules cannot concentrate the urine, so osmolality is usually < 350 .

Urine Na^+ is > 40 (however, if reabsorption of water is significantly affected, the urine Na^+ will become dilute).

$\text{FE}_{\text{Na}} > 2\%$. However FE_{Na} can be **low** in **contrast-induced nephropathy**.

Casts in the urine are the hallmark finding: **muddy brown “dirty” granular casts** (nonspecific but very sensitive) and epithelial cell casts ([Image 4-2](#), [Image 4-3](#)). Sometimes tubular epithelial cells are seen. But the urine sediment can be normal.

If the patient is volume-contracted as a cause for ATN, then the above labs will be more consistent with a prerenal picture.

TREATMENT OF ATN

Initial management of ATN includes treating the precipitating cause and any hyperkalemia. Maintain normovolemia and nutritional support, which decreases catabolism. Discontinue nephrotoxins.

Oliguric ATN usually resolves in 1–4 weeks. Note that oliguria is **not** required for the diagnosis of ATN. If oliguric, patients with ATN are more prone to becoming **hyperkalemic** and volume-overloaded, so dialysis is typically initiated earlier.

ATN AND RHABDOMYOLYSIS

Rhabdomyolysis is muscle degradation that results in the release of muscle enzymes, myoglobin, and electrolytes into the bloodstream. All of the following are causes:

- Crush injuries (compartment syndromes), coma, or traumatic immobilization
- Prolonged surgeries

- Strenuous exercise such as a marathon run or football in extreme heat
- Generalized seizures
- Heat stroke
- Severe volume contraction
- Drugs: cocaine, amphetamines, statins, colchicines, anesthetics causing malignant hyperthermia, neuroleptic malignant syndrome
- Infections: usually viral, especially influenza A and B
- Endocrinopathies: DKA, hypothyroidism, hyperthyroidism, and pheo
- Electrolyte abnormalities: hypokalemia, hypophosphatemia (in alcoholics during refeeding)

Patients present as a result of the underlying cause and/or with muscle pain and cola-colored urine. Labs show **increased CPK** ($> 100,000$ IU/L) with nonspecific increases in AST and ALT. It is important to be sure that there is no component of prerenal azotemia contributing to the AKI. Creatinine is usually elevated. Hyperkalemia, hyperphosphatemia, increased uric acid, and hypocalcemia are common complications. U/A shows muddy brown casts consistent with ATN. The urine is colored brown due to myoglobin pigment. The urine tests positive for blood, but no RBCs are visible in the sediment.

Rhabdomyolysis-associated **hypocalcemia** results from 2 mechanisms: 1) decreased production of $1,25\text{-(OH)}_2\text{-D}$ due to renal injury and 2) hyperphosphatemia due to both renal injury and tissue breakdown. In recovery, patients can have significant hypercalcemia from secondary hyperparathyroidism (among other causes). For this reason, do not treat hypocalcemia unless it is severe or the patient is symptomatic.

Start treatment as soon as possible with isotonic fluid resuscitation and forced diuresis with alkalinization of the urine to prevent the myoglobin-induced tubular

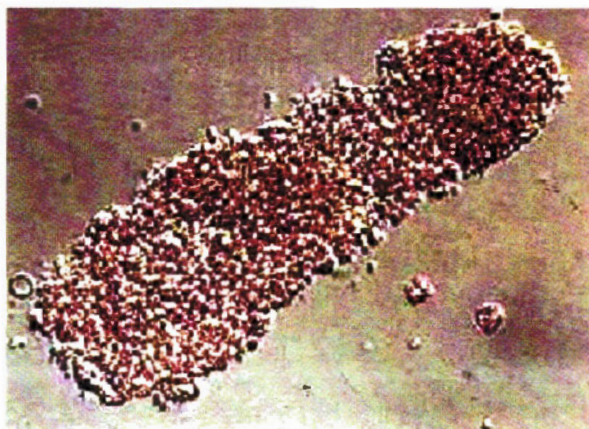


Image 4-2: Coarse granular (dirty brown) cast

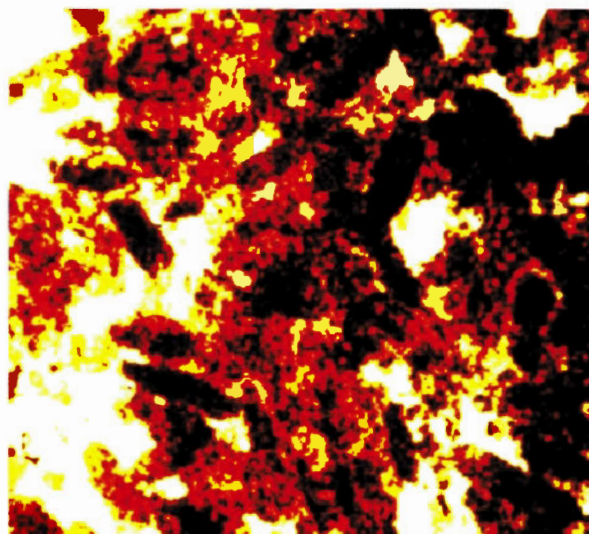


Image 4-3: Coarse granular casts

Quick Quiz

- What are the lab findings in ATN?
- What are the lab findings in rhabdomyolysis?
- Characterize the clinical presentation of acute interstitial nephritis.
- The biopsy picture of AIN due to NSAIDs resembles which glomerulonephropathy?

damage. Watch out for hyperkalemia. Dialysis is used in severe cases.

Hemoglobinuria has urine findings similar to those seen in rhabdomyolysis. Hemoglobin can be released from severe intravascular hemolysis. It also can cause ATN—not due to toxicity, but rather mechanical obstruction. Treatment is the same as that for rhabdomyolysis.

INTERSTITIAL DISEASE

OVERVIEW

Interstitial disease is caused by invasion of the interstitium. It can be acute or chronic. Both situations are usually caused by drugs.

Tubular and interstitial diseases have only **slight** proteinuria (< 1–1.5 g/d), and they may cause renal tubular acidosis (RTA).

ACUTE INTERSTITIAL NEPHRITIS

Acute (or allergic) interstitial nephritis (AIN) is most often a drug-induced **hypersensitivity** reaction that variably presents with fever, eosinophilia, and rash. Only 10% of patients have all 3. More often, presentation is lethargy and nausea/vomiting. Autoimmune diseases and some rare infections (*Legionella*) also cause AIN and often present as renal disease in an asymptomatic patient.

Most commonly implicated drugs include: NSAIDs, antibiotics, proton pump inhibitors, cimetidine, thiazides, and allopurinol. AIN is an idiosyncratic response to the drug and usually is not related to the amount or duration of use.

The most common antibiotic culprits:

- Beta-lactams
- TMP/SMX
- Rifampin
- Ciprofloxacin and, less often, other fluoroquinolones

NSAID-induced AIN is different in that the NSAIDs are typically ingested for months before symptoms occur. Rash, fever, and eosinophilia are frequently absent. Contrary to all other types of AIN, NSAID-induced AIN

usually causes **nephrotic-range proteinuria** and glomerular changes consistent with those of **minimal change disease**. Acute interstitial nephritis also can be caused by sarcoidosis, SLE, Sjögren's, transplant rejection, and infection (e.g., pyelo, *Legionella*, streptococci).

The urine sediment in AIN contains few red cells, white cells +/- WBC casts, and mild protein (< 1 g/day, if quantitated). Red cell casts are usually not seen. The Hansel stain may show urinary eosinophils. Peripheral blood eosinophilia is sometimes observed in severe cases. FE_{Na} is usually > 1%. NAGMA and Fanconi syndrome are not uncommon if the proximal tubules are significantly damaged.

Treatment includes discontinuing the offending drug and observing the patient. Recent data suggest a potential benefit for steroids if the diagnosis is confirmed (usually requires renal biopsy first).

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis is caused by:

- Drugs: chronic analgesics, lithium, cyclosporine, cisplatin, and Chinese herbs
- Hypertension
- Heavy metals (especially lead and cadmium)
- Obstruction
- Infections: reflux nephropathy, tuberculosis
- Sarcoidosis
- Sjögren disease
- Sickle cell disease
- Multiple myeloma

Chronic analgesic use had been one of the most common causes but phenacetin, a key ingredient, was removed from most OTC meds in the U.S. market. Since then, we rarely see this disease in spite of the other causes. Acetaminophen is the major metabolite of phenacetin, and it is unclear whether acetaminophen alone carries specific risk when used as a chronic analgesic. Combining acetaminophen with aspirin, however, is definitely associated with an increased risk of papillary necrosis—especially if it's further combined with mixtures containing caffeine or codeine. Chronic use of NSAIDs is associated with renal failure in some patients, but the association here is not as strong as with phenacetin and acetaminophen.

Analgesic-abuse nephropathy typically occurs in a patient with a history of frequent pain and presents with a low urine specific gravity, minimal proteinuria, sterile pyuria, and an elevated creatinine. Papillary necrosis is the most common ultimate consequence. A noncontrast CT of the kidneys may show the papillary necrosis, but not always. Treatment is supportive, with discontinuation of offending analgesics.

Although rare now, patients can be exposed to lead via their **occupation** (working with batteries, solder, cabling, ceramics, tin), drinking “**moonshine**” (yes, people still do this), taking alternative **herbal medications** from India and China, eating from **lead-glazed plates** or **cookware**, and smoking **marijuana**. Nephropathy may develop after years of high-level exposure and presents as azotemia, a tiny bit of proteinuria, hyperuricemia, and a bland urine sediment. Patients may have a comorbid crystalline arthropathy, termed “**saturnine gout**.” Diagnosis is made by noting the potential exposure history and measuring the serum lead level.

Remember that lithium can also cause nephrogenic DI as well as chronic interstitial nephritis.

An unusual kind of renal interstitial fibrosis can occur in the setting of Chinese herbs ingested as weight-loss agents, specifically the ingredient **aristolochic acid**.

GLOMERULAR DISORDERS

OVERVIEW

The glomerulus is a specialized capillary plexus surrounded by the Bowman capsule (**Image 4-4**). The capillary walls **filter** blood, allowing an ultrafiltrate of the plasma to pass into the Bowman capsule, which collects the ultrafiltrate in the tubules for further processing. Recall the diagram (**Figure 4-2**) of the collecting system on **page 4-13**.

The wall of the glomerulus filters with:

- Endothelial cells
- The glomerular basement membrane (**GBM**)
- Slit pores between the epithelial cell foot processes

Glomerular diseases primarily affect the glomerular apparatus only and are collectively termed “glomerulonephritides.” Glomerular diseases can be divided into 2 patterns, based on clinical presentation and mechanism of disease:

- 1) **Nephritic**: an acute or subacute, potentially reversible, inflammatory process that presents with hematuria, proteinuria (usually < 2 g/day), +/- RBC casts.

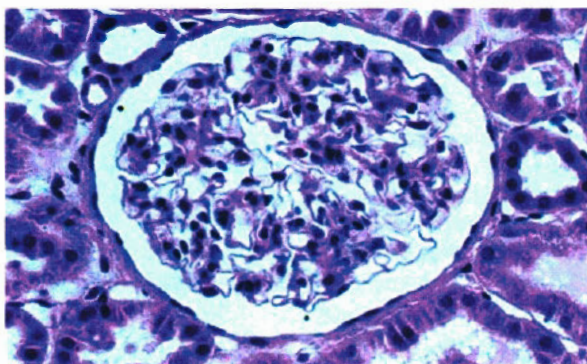


Image 4-4: Normal glomerulus

Disease can be focal and mild (active sediment without hypertension or edema) or diffuse and severe (active sediment with heavy proteinuria, renal failure, hypertension, and edema).

- 2) **Nephrotic**: a noninflammatory process that presents with > 3 g/day proteinuria and edema +/- urine oval fat bodies, but without red cells and casts in the urine sediment; renal function may be preserved. **Hypercholesterolemia**, **hypertension**, and **hypoalbuminemia** are features.

Know that patients with glomerular disease typically have either a nephritic or nephrotic presentation; however, both presentations can occur in patients with SLE or MPGN (membranoproliferative glomerulonephritis).

The causes of glomerular disease can be either primary renal (usually idiopathic) or systemic. Somewhat reliably, the renal pathology can be predicted based on the pattern of presentation and the patient's age. **Table 4-11 on page 4-38** is helpful to remember the most common causes of glomerular disease for each age group. **Table 4-12 on page 4-40** is provided as a major summary. In clinical practice, however, a step-wise approach to diagnosis is followed, which we will lay out on the following pages.

In progressive glomerulonephritis associated with worsening kidney injury, the **glomerulus** is the main site of pathology, but the **tubules** and **interstitium** are always affected as well. Therefore, clinical presentation of the progressive GNs will reflect disease in multiple locations.

A few other categories of glomerulonephritides are useful to help remember the more common and frequently tested causes:

- Pulmonary-renal syndromes (Goodpasture's, granulomatosis with polyangiitis [previously called “Wegener's”], microscopic polyangiitis, Churg-Strauss, Henoch-Schönlein purpura, cryoglobulinemia)
- Basement membrane syndromes (anti-GBM disease [also called Goodpasture's], Alport's, thin basement membrane disease)
- Infectious disease syndromes (post-strep GN, endocarditis, HIV, HBV, HCV, syphilis, malaria)
- Other: antiphospholipid syndromes, HSP, cryoglobulinemia, amyloidosis

Achieve definitive diagnosis of all glomerular diseases with a renal biopsy, though typical diabetic nephropathy is almost always diagnosed clinically.

It can be hard to determine whether isolated microscopic hematuria is coming from the kidney or lower urinary tract, but hematuria with proteinuria and RBC casts is likely to be of renal origin. Nonrenal hematuria could be caused by malignancies in the urinary tract

Quick Quiz

- Characterize the differences between nephritic and nephrotic urine sediments.
- What is the definition of nephrotic-range proteinuria?

(bladder cancer), kidney stones, or urinary tract infections. Patients with sickle cell trait may also have isolated hematuria. **Red cells casts**, however, are **definitive** for GN.

Refer to **Figure 4-3**, **Table 4-11**, and **Table 4-12** as you go through this section.

NEPHRITIC vs. NEPHROTIC

In the **nephritic** pattern, there is **variable proteinuria**, and an “**active**” urine sediment. An “**active sediment**” is urine that contains proteinuria, red cells > 10/hpf, white cells—and often red cell, white cell, and granular casts.

Casts **always** originate in the tubules. Know the following:

- **Red cell casts** are a very specific finding. They are seen only in glomerulonephritis.
- **White cell casts** are typically seen in pyelonephritis.

- **Granular casts** can be nonspecific; in the setting of acute kidney injury with an appropriate clinical picture, they are characteristic of acute tubular necrosis.
- **Waxy casts** typically indicate advanced renal disease.
- In patients with a lot of proteinuria, free fat can assemble into a cast (called a **fatty cast**), or fat can suspend in the urine as droplets.
- Hyaline casts do not indicate disease and are seen with concentrated urine.

Nephrotic urine reflects defects in the selectivity of glomerular ultrafiltration, even though there is little inflammation. This can be due to changes in the charge or size of the selective barrier in the glomerular basement membrane (GBM). In nephrotic syndrome, there is typically heavy proteinuria, and urine fat may be visible as oval fat bodies, fatty/waxy casts, and renal tubular cells with lipid droplets. The urine sediment is usually normal except for the fat.

Nephrotic-range proteinuria is > 3.5 g/d (or 40–50 mg/kg/d). Because of this protein loss, nephrotic patients tend to have **hypoalbuminemia** (with 2° **edema**), **hypogammaglobulinemia** (with a tendency for infections with encapsulated organisms, especially *H. influenzae* and *S. pneumoniae*), loss of thyroid and iron-binding globulins (so low total thyroxine and iron levels), and loss of **antithrombin III** (so they have a hypercoagulable state and are at risk for **pulmonary emboli** and **renal vein thrombosis**).

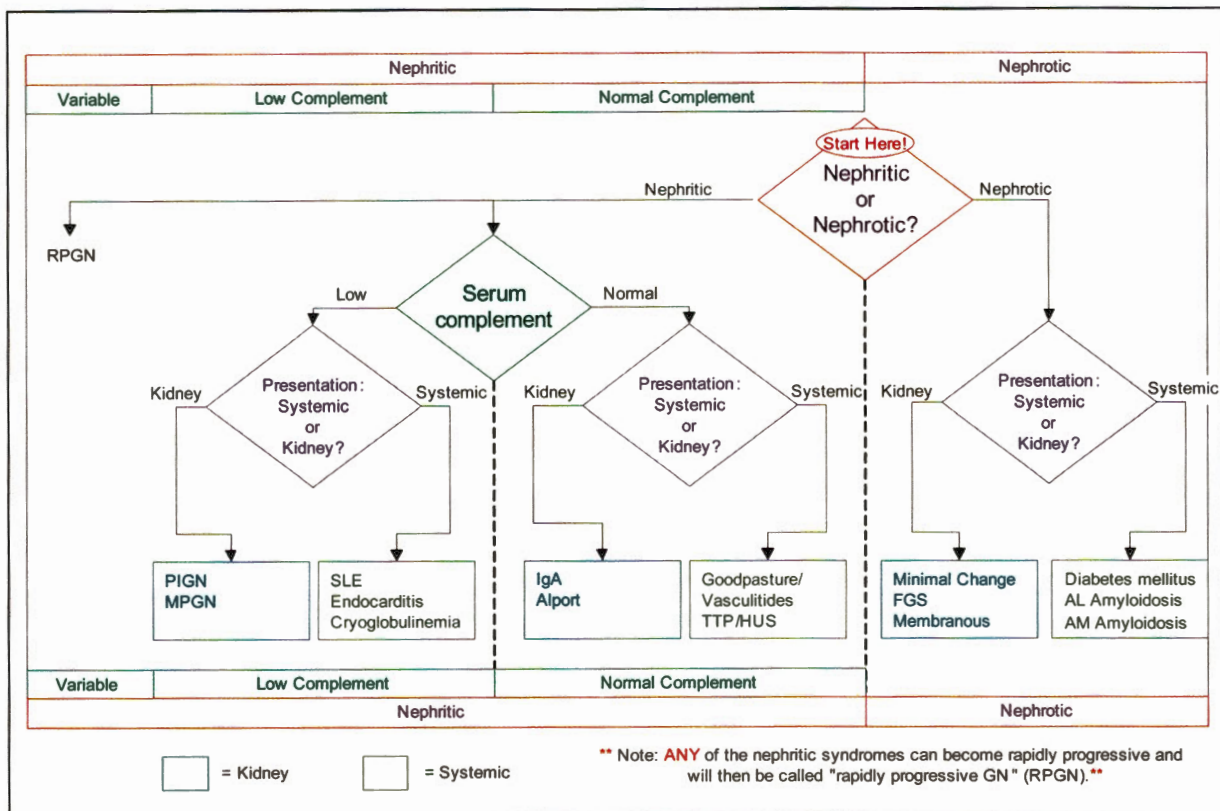


Figure 4-3: A Strategy for Workup of the Glomerular Disorders

Nephrotic patients also have **hyperlipidemia**. When the albumin is very low, these patients often have severe **peripheral edema**, **pleural effusions**, and even **ascites**—yet they do not have pulmonary congestion/edema unless they have heart failure. This is because the pulmonary interstitium loses albumin at the same rate as the blood, so there is not a big osmotic differential.

A strategy that helps classify the glomerular diseases (use this!):

- 1) Is the urine **nephritic** or **nephrotic**? If the urine is nephritic, is the complement **low** or **normal**?
- 2) Does the patient present with a **systemic** disorder by history and physical exam, or is the presentation primarily a **kidney** disorder (e.g., edema, hypertension only)?

While reading below, follow along in **Figure 4-3**. Know this flowchart! It gives structure to this otherwise quite confusing set of renal problems.

NEPHRITIC SYNDROMES

Complement in Nephritic Syndromes

Nephritis from lupus is associated with hypocomplementemia, but complement levels are usually normal in cases of pulmonary-renal vasculitis.

C3 is always low for 6–8 weeks with postinfectious GN and is frequently low with idiopathic membranoproliferative GN and most of the systemic causes of MPGN (endocarditis, cryoglobulins, and HBV).

As soon as you see a **nephritic** picture, the **first** test you do is a **complement** level. Even if the patient presents with a history of classic postinfectious glomerulonephritis, still measure complement levels first!

Nephritic with Low Complement — Primarily Kidney Presentation

Nephritic/low/kidney:

- Postinfectious GN (PIGN)
- Membranoproliferative GN (MPGN)

Postinfectious GN

Usually, PIGN is caused by group A beta-hemolytic streptococcal infections of the skin or throat (occasionally associated with other infectious causes). This entity has been called “post-strep GN” (PSGN).

Symptoms include gross hematuria and/or edema and occur 1–6 weeks after the initial illness (average 10 days post-throat infections, 2–4 weeks after skin infections). The “**latency period**” is a diagnostic key and is used in differentiating PIGN from IgA nephropathy, wherein the GN coincides with or begins within 3 days of the viral illness. Cultures of throat and skin variably grow beta-hemolytic streptococci.

Antistreptococcal antibodies aid in the diagnosis:

- Antistreptolysin O (ASO) titer
- Antideoxyribonuclease B (anti-DNase B) titer
- Antihyaluronidase titer

Know that an ASO titer generally remains elevated for **several weeks** after a strep infection; the anti-DNase B titer for several months. Complement levels remain low for 6–8 weeks.

PIGN is caused by an antibody-antigen reaction, with the source of the antigen being the infecting agent. Renal biopsy shows immune deposits (IgG, M, and complement) in the subendothelial and subepithelial regions (termed “humps”) + invasion of the glomerulus with neutrophils. In children, renal biopsies are rarely performed because the diagnosis can usually be made via the clinical history + measurement of complement levels and antistreptococcal antibodies. These infections are rare in adults, though, so an adult with this presentation will probably get a renal biopsy.

PIGN rarely progresses to severe renal failure. Patients improve with supportive care and treatment of the underlying infection with standard antibiotics. Most children recover completely in 6–8 weeks, but adults may not have complete recovery.

Summary of PIGN: **reversible**, **bloody urine** remote to group A streptococcal skin or throat infection (rarely, other infections); **low complement** for 6–8 weeks; variably positive **antistreptococcal antibody titers**; subendothelial and subepithelial immune “humps” on renal biopsy; treat the infection; good response in most.

Membranoproliferative GN (MPGN)

MPGN can be idiopathic and cause isolated kidney disease, but more commonly, it is associated with **systemic** diseases, primarily lupus and HCV-associated cryoglobulinemia. Usually, the MPGN pathology (whether idiopathic or associated with systemic disease) is marked by activation of complement, and about 50% of the time the complement levels will be low. While the disease typically presents as a nephritic picture, nephrotic-range proteinuria is not uncommon.

The low C3 in PIGN returns to normal after 2–3 months; but in patients with MPGN, it stays low indefinitely. This is useful: If you initially suspected PIGN and C3 stays low > 3 months, suspect MPGN instead, and get a renal biopsy! Treatment is aimed at the underlying disease if it can be identified. This includes plasmapheresis for cryoglobulinemia. Progression to kidney failure is common.

Nephritic with Low Complement — Systemic Presentation

Nephritic/low/systemic:

- Systemic lupus erythematosus (SLE). Know also that SLE can produce almost any type of glomerular disease (nephritic or nephrotic).

Quick Quiz

- What are the systemic complications of nephrotic syndrome?
- What are the complement levels in patients with post-infectious glomerulonephritis?
- Post-strep glomerulonephritis can occur after strep infections at which sites?
- Symptoms of GN due to strep start how long after the original illness?
- What infections are associated with development of MPGN?
- When does the GN due to IgA nephropathy present, relative to an inciting viral illness?
- What are the findings on renal biopsy in patients with IgA nephropathy?
- Endocarditis.
- Cryoglobulinemia in this situation is usually due to HCV, myeloma, or Waldenström macroglobulinemia.

Nephritic with Normal Complement — Primarily Kidney Presentation

Nephritic/normal/ kidney:

- IgA nephropathy
- Alport syndrome
- ANCA + glomerulonephritis (microscopic polyangiitis)

IgA Nephropathy

Sometimes called “mesangial proliferative GN” or Berger disease (do not confuse with Buerger disease—thromboangiitis obliterans). Worldwide, this is the most common GN; it is more common in Asians and males.

IgA nephropathy has a wide range of presentations, from gross hematuria coincident with or immediately following a URI, to microscopic hematuria with proteinuria and progressive disease, to nephrotic syndrome or RPGN (page 4-39). The hematuria seen in IgA nephropathy commonly occurs either during a viral illness or just after exercise. There is **no latent period** between infection and appearance of GN, as with PIGN. This is an important distinguishing feature!

The antibody-antigen interaction in this disease causes immune complex deposition of IgA and C3 in the mesangial matrix and skin. Although C3 is deposited, there are usually normal serum complement levels.

IgA nephropathy is more progressive in patients with proteinuria and is relatively innocuous in those with isolated hematuria. The only way to make this diagnosis is

with renal biopsy, which is performed in patients with a more severe presentation. Biopsy shows deposits of IgA and complement in the mesangium and in the glomerular capillaries on immunofluorescence staining. Light microscopy shows isolated proliferation in the mesangium (with crescent formation, if the disease is severe), [Image 4-5](#).

Other diseases may deposit IgA in the mesangium but are not classified as “IgA nephropathy,” such as lupus nephritis and Henoch-Schönlein purpura. Clinical presentation in these illnesses differentiates the disease from basic IgA nephropathy. Some illnesses are associated with IgA deposition but without obvious glomerular injury, such as HIV/AIDS, celiac disease, and end-stage liver disease. These presentations are called “secondary IgA nephropathy.”

Prognosis for IgA nephropathy is tied to serum creatinine, blood pressure, and amount of proteinuria. Prognosis is good if these values are normal, but it is much worse if any of these are abnormally elevated. 50% of patients with proteinuria have inexorably progressive renal disease.

Patients who maintain normal renal function can be observed. ACEIs or ARBs should be used for proteinuria and progressive disease; corticosteroid therapy +/- other immunomodulators are sometimes used in severe cases. Statins and fish oil have also been used to modulate the risks of atherosclerosis and also to prevent progression, but their true role is not defined.

Hereditary Nephritis (Alport Syndrome)

Alport syndrome is a hereditary (usually X-linked) syndrome with chronic glomerulonephritis +/- nerve deafness and congenital eye problems involving lenses, retinas, and corneas. These patients have a defect in the α -3 subunit of Type IV collagen. Renal biopsy confirms the diagnosis in patients with suspected disease. The hallmark finding is a split lamina densa (part of the GBM) visible on electron microscopy. Genetic testing is also being done. Treatment includes ACEIs or ARBs.

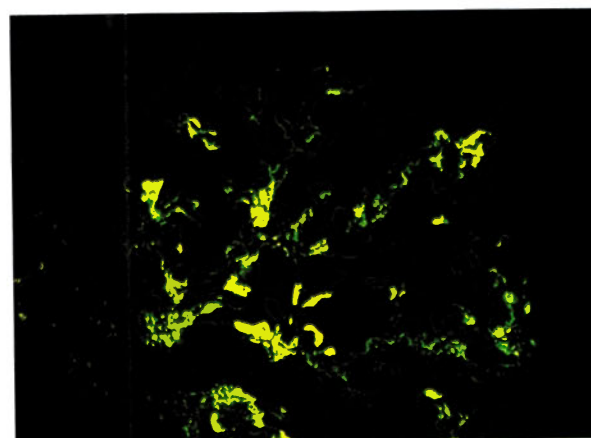


Image 4-5: Immunofluorescent microscopy in IgA nephropathy

Courtesy of Siram S. Narisipur, MD

Table 4-11: Characteristics of Glomerulonephritides

Pattern of Presentation	Age at Presentation		
	Childhood	15–40 years	> 40 years
Focal, nephritic	PIGN IgA HSP	IgA SLE	IgA
Diffuse, nephritic	PIGN MPGN	PIGN SLE MPGN RPGN	RPGN Vasculitis cryoglobulinemia PIGN
Nephrotic	Minimal change FGS IgA (rarely nephrotic)	FGS Minimal change Membranous Diabetes Preeclampsia PIGN (rarely nephrotic)	FGS Membranous Diabetes Minimal change IgA (rarely nephrotic) Amyloidosis Light chain deposition

Nephritic with Normal Complement — Systemic Presentation

Nephritic/normal/systemic:

- Anti-GBM disease
- Vasculitides
- TTP/HUS

Anti-GBM Disease

Anti-GBM disease is a broad term that encompasses an acute GN with evidence of anti-GBM antibodies in the serum +/- pulmonary hemorrhage.

When **pulmonary hemorrhage** is present (common; occurs in 70% of patients), the disease is called **Goodpasture's**. Otherwise, it's called anti-GBM disease.

Younger, male patients are more likely to present with Goodpasture's and older females with idiopathic anti-GBM disease. Despite previous classifications of anti-GBM diseases, this disease is not a vasculitis. Patients present with an active urine sediment and hemoptysis with dyspnea if they have Goodpasture's. If fever or weight loss is present with a GN, consider the vasculitides (discussed next).

In anti-GBM diseases, antibodies that attack the glomerular (and sometimes pulmonary) basement membrane(s) are formed in response to an unknown stimulus. Goodpasture's typically presents as an RPGN (discussed below).

Renal biopsy makes the diagnosis by revealing anti-GBM **IgG** deposited in a **linear** fashion along the GBM. Anti-GBM antibodies can be measured in the serum, and, when present, make the diagnosis. Sensitivity of the serum antibody test is not 100%, so when these antibodies are absent, renal biopsy should be performed. The biggest challenge is differentiating granulomatosis with

polyangiitis (previously "Wegener's") or other forms of vasculitis from Goodpasture's. These disorders are more likely to be c-ANCA-positive or have other serologic markers.

Treatment of Goodpasture syndrome is plasmapheresis (to remove the antibodies) with immunomodulation (steroids + cyclophosphamide). Prognosis depends on the extent of renal failure at presentation.

Vasculitides

The main vasculitides that commonly involve an acute GN include:

- granulomatosis with polyangiitis,
- microscopic polyangiitis,
- polyarteritis nodosa (PAN),
- Churg-Strauss, and
- Henoch-Schönlein purpura (HSP).

The first 4 are discussed in both the Rheumatology section, Book 3, and the Pulmonary Medicine section, Book 2. HSP is seen mostly in children. Kidney or skin biopsy findings in HSP are identical to the findings in IgA nephropathy, but HSP also affects the skin, GI tract, and joints. Patients may have abdominal and joint pains, erythema, urticaria, purpura, and hematuria.

Although these entities are vasculitic, complement levels are usually normal.

TTP / HUS

TTP and hemolytic uremic syndrome are discussed in the Hematology section, Book 4.

Quick Quiz

- What is the difference between Goodpasture syndrome and anti-GBM disease?
- How are anti-GBM diseases diagnosed?
- RPGN has what hallmark finding on renal biopsy?
- What are the 4 categories of RPGN, based on underlying mechanisms?
- What is the empiric treatment for RPGN?

Rapidly Progressive GN (RPGN)

The most aggressive syndrome of AGN is RPGN. This term refers to any form of acute GN that progresses rapidly (days–weeks) and is associated histopathologically with the hallmark subepithelial **crescent** inside Bowman's capsule. Hence, you can have RPGN with high or low complement, or RPGN that presents with systemic disease or as a primary kidney disorder.

Always consider RPGN if a patient presents with severe and progressive renal failure of recent onset. Once RPGN is diagnosed, you need to quickly determine and treat the underlying disease.

In RPGN, creatinine is usually > 3 mg/dL. The urine has **protein**, **red cells**, and **RBC casts**. Other complaints by the patient are dependent on the cause of the RPGN. There are 3 major pathogenic causes of RPGN:

- **Type 1** is due to anti-GBM antibodies (Goodpasture's).
- **Type 2** is due to immune complex deposition (IgA deposits; ANA in lupus; cryoglobulins; antibodies against an infectious agent, such as streptococci).
- **Type 3** has no evidence of immune deposits (termed "pauci-immune"); many of these cases are ANCA+, anti-MPO+ and will be diagnosed as **granulomatosis with polyangiitis** or **microscopic polyangiitis**. (See the Rheumatology section, Book 3, for discussion of ANCA and myeloperoxidase antibodies.)

Evaluation of the patient with RPGN should attempt to make a **rapid histopathologic diagnosis** and measure **ANCA** titers:

- If there is pulmonary hemorrhage, a linear staining of IgG along the GBM on kidney biopsy, and a high titer of serum anti-GBM antibodies, the disease is **Goodpasture syndrome**. Again, +anti-GBM antibodies but no pulmonary hemorrhage is just called "anti-GBM disease."
- If patient has ENT manifestations, lung findings, and is c-ANCA positive—think **granulomatosis with polyangiitis**.
- If there are no systemic features, immunofluorescence is negative on renal biopsy, and p-ANCA is positive,

the patient has **pauci-immune GN** (otherwise known as microscopic polyangiitis).

- If RPGN is caused by lupus nephritis, cryoglobulinemia, or PIGN, there will be characteristic immunofluorescent and other findings on renal biopsy to establish the underlying cause.

Treat RPGN empirically with high-dose methylprednisolone, then prednisone + cyclophosphamide +/- plasmapheresis (if pulmonary hemorrhage). Once the biopsy and other diagnostic results are available, definitive treatment can be given based on underlying disease (e.g., cyclophosphamide is always given to SLE and granulomatosis with polyangiitis; and plasmapheresis to Goodpasture's and cryoglobulinemia).

Summary of RPGN: **rapidly progressive** renal failure with **nephritic** urine sediment; 3 categories; renal biopsy shows **crenents**; think Goodpasture's, lupus, granulomatosis with polyangiitis, and immune-complex disease; treat empirically with steroids and cyclophosphamide, then focus on treating underlying disease; plasmapheresis for anti-GBM and cryoglobulinemia.

NEPHROTIC SYNDROME

Overview

The following glomerulonephritides cause nephrotic-range proteinuria.

Nephrotic syndrome, regardless of cause, is associated with an increased risk of infections and a hypercoagulable state—because of the urinary loss of immunoglobulins and antithrombin III.

Nephrotic — Primarily Kidney Presentation

Nephrotic/kidney:

- Minimal change disease
- Focal and segmental glomerulosclerosis (FGS)
- Membranous nephropathy

Minimal Change Disease (MCD)

MCD accounts for 10–15% of nephrotic syndromes in adults. Pathologic cause seems to be related to T-cell dysfunction, resulting in fusion of the foot processes in the glomerular capillary walls. This makes for a leaky membrane and significant proteinuria.

The vast majority of MCD is idiopathic, but it has been associated with several drugs and diseases. Especially know the following associations:

- Drugs (NSAIDs, lithium, and sulfa)
- Lymphoma (both Hodgkin's and NHL)

Patients present with **anasarca** or severe peripheral **edema** that develops over several weeks and **without** HTN. Adults may have renal failure that usually improves with treatment.

Table 4-12: Summary Table of Glomerulonephritides

Classification / Complement Level	Name	Presentation	Urine	Notes	Treatment
NEPHRITIC SYNDROME Primarily <i>Kidney</i> Presentation	Low	PIGN	Red cells Proteinuria Red cell casts +/- white cell casts	Latent period between infection and symptoms. Complements return to normal after a short period. Check for antibodies of antecedent strep infection.	Treat the infection.
		MPGN		Complements stay low > 3 months.	No good Rx; steroids; frequent renal failure.
	Normal	IgA (Mesangial proliferative)		Most common GN	Observation ACEI or ARBs Steroids/cytotoxics
		Alport		X-linked recessive	ACEIs or ARBs
NEPHRITIC SYNDROME <i>Systemic</i> Presentation	Low	SLE Endocarditis Cryoglobulinemia HBV		MPGN pathology common	Treat the cause.
	Normal	Goodpasture's Vasculitis TTP/HUS			Treat the cause.
NEPHRITIC SYNDROME RPGN	Variable	1. Anti-GBM 2. Immune complex 3. Pauci-immune 4. Double Ab		Crescents on renal biopsy; check ANCA and anti-GBM ab; consider ANA, anti-ds-DNA, cryoglobulins, anti-streptococcal Ab	High-dose methylprednisone → prednisone + cytotoxics +/- plasmapheresis
NEPHROTIC SYNDROME Primarily <i>Kidney</i> Presentation		Minimal Change Disease	> 3 g/d proteinuria Oval fat droplets Edema Hyperlipidemia	Loss of foot processes on electron microscopy	Steroids +/- cytotoxics
		FGS	Complications: DVT Bacterial infections	Possible variant of minimal change disease	Steroids Cyclosporine ACEIs or ARBs
		Membranous			Treat underlying disease Steroids +/- cytotoxics ACEIs or ARBs
NEPHROTIC SYNDROME <i>Systemic</i> Presentation		Diabetes	Diabetic with nephrotic-range proteinuria	Commonest secondary cause of nephrotic syndrome; eye disease usually precedes kidney disease.	ACEIs or ARBs +/- low-protein diet; control of blood glucose, BP, and lipids
		AL amyloidosis AM amyloidosis	Injection drug use Myeloma		Treat underlying disease.

Quick Quiz

- What drugs and diseases are associated with Minimal Change Disease?
- “Maltese crosses” under polarized light are seen in the urine sediment of patients with what process? (No—not *Babesia*; this is nephrology, not ID.)
- FGS is found in what patient groups?
- Solid tumors are associated with which glomerular disease?

Urine sediment may show oval fat bodies (Image 4-6) that also appear as “Maltese crosses” under polarized light.

Adult diagnosis is made by renal biopsy, which shows **no change** in histology on light microscopy and absence of immune deposits on immunofluorescence. Electron microscopy shows loss of epithelial foot processes, though this finding may be seen in any disorder that causes nephrotic syndrome.

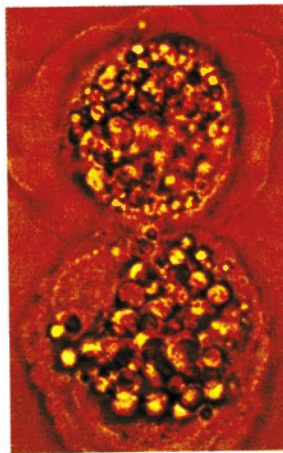


Image 4-6: Oval fat droplets on light microscopy

Courtesy of Sriram S. Narasimhan, MD

All adults with nephrotic syndrome should undergo renal biopsy for diagnosis. Treat MCD initially with steroids. Adults are more likely to be either steroid-dependent or -resistant and require cyclophosphamide or cyclosporine. Children are typically treated empirically with corticosteroids, with renal biopsy performed **only** if the expected response to steroids does not occur.

Summary: **nephrotic-range** proteinuria, children, **NSAIDs**, **lymphoma**, **atopy**, risk of **infections** and **DVT**, loss of foot processes, Maltese crosses, steroids, **generally very good** prognosis.

Focal and Segmental Glomerulosclerosis (FGS)

FGS has become the most common cause of idiopathic nephrotic syndrome in African-Americans and is the most common glomerular process causing end-stage kidney disease in the U.S. Especially consider FGS if there is a history of HIV/AIDS, heroin use (especially in African-Americans), obesity, sickle cell disease, hematologic malignancies, or chronic vesicoureteral reflux. FGS is the most common cause of nephrotic syndrome in patients with HIV and is the cause of “HIV-associated

nephropathy.” However, the majority of FGS are idiopathic. It is important to distinguish between primary FGS and the secondary causes (e.g., heroin) because the primary disease frequently responds to steroids—secondary disease, less so.

FGS is similar to minimal change disease in that there is diffuse **foot process loss**; however, there is additional sclerosis limited to **segments** of the glomeruli (especially juxtamedullary). Unlike minimal change disease, these patients often present hypertensive as well as nephrotic. 50% will have a reduction in kidney function at diagnosis.

These patients have slowly progressive renal failure. Those **not** responding to treatment **require dialysis** within ~ 5–10 years.

Initial treatment of primary FGS includes ACEIs/ARBs and high-dose steroids for extended periods in order to induce remission. Patients without remission have a poorer prognosis. Long-term treatment can improve the prognosis and keep up to 70% of patients disease-free.

Secondary FGS is treated with ACEIs or ARBs and therapy directed at the underlying illness (such as HIV). Severe proteinuria and reduction in GFR at diagnosis are associated with worse prognosis.

Summary: **nephrotic-range** proteinuria, loss of **foot processes** and **focal sclerosis**, **African-Americans**, young hypertensive, **AIDS**, **heroin**, obesity. Treat primary disease with long-term steroids.

Membranous Nephropathy

Idiopathic (primary) membranous nephropathy is a common cause of non-diabetic nephrotic disease in adults, especially in Caucasian males > 40 years of age. Secondary causes include:

- Chronic **infections** (especially chronic HBV)
- Several **drugs** (NSAIDs, penicillamine, and gold)
- Underlying **solid tumors** (Tumors are usually obvious.)
- Autoimmune thyroiditis and SLE (Consider this cause if membranous presents in a young female.)

Patients with membranous nephropathy present with a gradually worsening nephrotic syndrome, and 50% of patients will have red cells in the urinary sediment (without RBC casts). Most patients will have normal blood pressure and renal function at diagnosis.

Renal biopsies should be done in all cases of nephrotic syndrome when the underlying cause is not obvious (e.g., diabetes). Renal biopsy shows GBM subepithelial IgG and C3 deposits on immunofluorescence. Electron microscopy shows subepithelial deposits on the GBM with loss of overlying foot processes. The GBM is also expanded because new matrix is laid down between the subepithelial deposits.

Patients will spontaneously improve (up to 30% after 5 years), improve completely or somewhat with treatment, or progress to dialysis (14% at 5 years). Patients with more severe proteinuria and/or reduced GFR have a worse prognosis, as do men > 50 years old. Secondary membranous will often improve with treatment of the underlying disease or discontinuation of any offending drugs.

Because some patients can have spontaneous remission, not all patients need to be treated immediately. Treat only those who present with higher levels of proteinuria and a low GFR. Optimal therapy appears to be corticosteroids plus a cytotoxic agent (cyclophosphamide or chlorambucil). Treat the proteinuria and hypertension with ACEIs or ARBs.

Summary: Nephrotic-range proteinuria, HBV, gold, penicillamine, solid tumors, SLE. Worse prognosis in men. If severe, treat with corticosteroids plus a cytotoxic agent.

Nephrotic — Systemic Presentation

Nephrotic/systemic:

- Diabetes mellitus
- Amyloidosis and multiple myeloma
- SLE (covered in Rheumatology section, Book 3)

Diabetic Nephropathy

Diabetic nephropathy is the most common systemic cause of nephrotic syndrome in adults. It may be associated with hyporeninemic hypoaldosteronism and Type 4 RTA.

The risk of nephropathy is the same, regardless of whether patients have Type 1 or 2 diabetes; and, in most cases, retinopathy precedes nephropathy (less rigorous association for T2DM).

The risk of developing nephropathy is multifactorial and is based on:

- age at diagnosis,
- genetics,
- race (increased risk in African-Americans, Hispanics, and the Pima Native American tribe),
- blood pressure,
- glomerular filtration rate (hyperfiltration in the first 5 years after diagnosis = higher risk),
- glycemic control,
- weight (obesity = increased risk),
- smoking, and
- oral contraceptive use.

Renal biopsy classically shows expansion of the mesangium, thickening of the GBM, and sclerosis of the glomeruli (termed the Kimmelstiel-Wilson lesion).

Diabetic nephropathy occurs in two phases. In the silent or preclinical phase, the first measurable change in renal function is microalbuminuria, which is albumin

too small to be detected on routine dipstick (30–300 mg/24 hr). It can be detected by measuring the random urine protein:creatinine ratio. More than 30 mg/24 hr (spot urine protein:creatinine > 0.03) represents a positive test. Test all diabetics yearly for microalbuminuria using the spot protein:creatinine, and, if results > 0.03 (equivalent to 30 mg/24 hr), treat with an ACEI or ARB even if normotensive.

The clinical phase is typically associated with nephrotic-range proteinuria, hypertension, and retinopathy. Control of hypertension (to < 130/80 with an ACEI or ARB) and glycemia definitely slow the rate of progression. While the American Diabetes Association added a recommendation to reduce protein intake in diabetics with chronic kidney disease (0.8–1.0 gm/kg body weight/day in early disease and 0.8 gm/kg/d in late disease), the use of low-protein diet in chronic kidney disease is controversial. Weight reduction and treatment of hyperlipidemia also seem to decrease risk.

Expert recommendations conclude that patients who have proteinuria in the setting of diabetes and retinopathy do not need to undergo kidney biopsy for diagnosis of a declining GFR. Diabetics without eye disease, however, should have a renal biopsy to exclude other glomerular causes of nephrotic syndrome. If red cells are present, the patient definitely should have a renal biopsy.

Know: As renal function decreases, insulin requirements decrease (2° to decreased metabolism by the kidneys).

Amyloidosis

Amyloidosis causes light chain nephropathy. Light chain nephropathy causes microscopic changes similar to those in diabetic nephropathy. So if you see a renal biopsy with very large hyaline-appearing nodular masses in the glomerulus, think of diabetic or light chain nephropathy. Congo-red stain of amyloid gives the glomeruli a unique “apple-green birefringence” when viewed with the polarizing microscope.

There are various causes and biochemical types of amyloidosis. Primary or “AL” amyloidosis can cause nephrotic syndrome as part of multisystem infiltration by monoclonal immunoglobulin light chains or in association with multiple myeloma (MM). The most common form of renal involvement in MM is “cast nephropathy,” but when nephrotic syndrome occurs in MM, it is likely due to amyloidosis. The MM light chain deposits do not have the unique staining with Congo-red dye.

Secondary or “AA” amyloidosis is seen in chronic inflammatory states, such as those seen in rheumatoid arthritis and familial Mediterranean fever (FMF). Amyloid nephropathy can also be caused by recurrent skin and soft tissue infections.

Other clues to amyloidosis include carpal tunnel syndrome and new-onset heart failure associated with nephrotic syndrome.

Quick Quiz

- Which RTA is associated with diabetic nephropathy?
- What is the classic finding seen on renal biopsy in a patient with diabetic nephropathy?
- What is the definition of microalbuminuria?
- When are glucocorticoids not used to treat nephrotic syndrome?

Treatment of Nephrotic Syndrome

General principles: Treatment of nephrotic syndrome depends on the underlying disease. Control of glomerular pressure is vital in **any** glomerular disease; increased intraglomerular pressure hastens disease progression. **ACEIs or ARBs** are best in decreasing intraglomerular pressure. They have been typically prescribed along with a low-protein diet—but benefit of the diet is uncertain. Use diuretics prn, but **be careful**—patients with nephrotic syndrome usually have difficulty maintaining intravascular volume; salt restriction and diuretics can precipitate prerenal failure. Note that glucocorticoids +/- cytotoxics are used in **most** nephrotic syndromes—**except** those caused by **amyloid** and **diabetes**. Anticoagulation is used if there is a significant risk of thrombosis. Be aware of the significant increased rate of infections and vaccinate accordingly.

ONCE MORE

Again: Hypocomplementemia **always** occurs in **PIGN** and **frequently** in **MPGN**. Low complement is also a feature in cryoglobulinemic GN, flares of SLE (which cause any glomerulonephritis), and bacterial endocarditis.

Hypocomplementemia **never** occurs in the nephrotic syndromes (minimal change disease, FGS, membranous nephropathy, diabetic nephropathy, amyloid nephropathy).

And again: Nephritic urine sediment is described as “active” (red cell casts and hematuria > 10 rbc/hpf) and is **usually seen** in IgA nephropathy (mesangial proliferative), early PIGN, MPGN, SLE, endocarditis, and cryoglobulinemia. RBC casts are **not** seen in the nephrotic syndromes: minimal change, FSG, membranous nephropathy, diabetic nephropathy, and amyloid nephropathy.

And again, urine sediment in renal disease:

- **Prerenal failure**: bland U/A; occasionally granular and/or hyaline casts.

- **Postrenal**: frequently is bland, may have blood; WBC casts if due to infection; sterile pyuria if due to papillary necrosis; never red cell casts.
- **Intrinsic renal**: ATN = dirty brown granular casts.

Glomerulonephritides: nephritic (hematuria with RBC casts and sometimes pyuria with WBC casts) and nephrotic (fat bodies). Interstitial nephritis: eosinophils, RBCs, WBCs, and WBC casts.

Remember: Use steroids in most nephrotic syndromes—except those caused by amyloidosis and diabetes. Many causes of nephritic syndrome require steroids with cytotoxics, especially RPGN.

OTHER DRUG-INDUCED NEPHROPATHIES

In patients with hyperreninemic or hyporeninemic states, NSAIDs can exacerbate the condition. Yes, that means NSAIDs can both increase and decrease renin. NSAIDs inhibit prostaglandins (PGs).

Dilation of the **afferent** arteriole and maintenance of glomerular perfusion pressure require prostaglandins; NSAIDs block this effect, but not significantly unless the patient already has a low-volume condition (e.g., low cardiac output). NSAIDs can also increase the likelihood of hypokalemia in this scenario by the same mechanism: (constricts afferent arterioles → ↓ GFR → ↑ renin → ↑ angiotensin → ↑ aldosterone → **hypokalemia**). This typically occurs only in patients who already have low-flow states (e.g., low cardiac output).

PGs are also necessary for renin release by the juxtaglomerular (JG) cells. NSAIDs block this—significantly only in low renin states. This effect will exacerbate the tendency for **hyperkalemia** in this hyporeninemic hypoaldosterone situation.

NSAIDs can also cause an acute or a chronic interstitial nephritis, usually with nephrotic-range proteinuria and papillary necrosis.

Chronic injection drug users are at risk for several types of kidney problems:

- Acute bacterial endocarditis causes either focal or progressive glomerulonephritis by **immune complex deposition** in the kidney.
- Endocarditis is associated with **emboli** that may result in renal infarction and hematuria.
- A chronically progressive **focal sclerosis** is occasionally seen in injection drug users.
- Injection drug users are at risk for **HIV** infection and subsequent HIV-associated nephropathy caused by FGS.

KIDNEY INJURY IN CANCER

To summarize cancer and AKI, here is a hodgepodge of facts that you should know.

AKI in cancer can be grouped into several categories:

- **Direct infiltration** by lymphoma, leukemia, or myeloma.
- **Obstruction**, particularly from pelvic and abdominal tumors; intratubular uric acid obstruction due to tumor lysis syndrome, methotrexate crystallization.
- **Glomerular** disease: minimal change disease, Hodgkin disease, membranous GN, solid tumors, amyloidosis from multiple myeloma.
- Mitomycin C-induced **hemolytic uremic syndrome**.

In patients with very high WBCs being treated with antimetabolites, give prophylaxis against acute urate nephropathy with **allopurinol**, maintain volume expansion, and **alkalinize** the urine. A new allopurinol alternative is **rasburicase**, for patients who cannot take allopurinol. See the Hematology section, Book 4.

CHRONIC KIDNEY DISEASE

OVERVIEW

Current practice guidelines have changed the term “chronic renal failure” to chronic kidney disease (CKD). CKD is defined as either of the following:

- Kidney damage > 3 months, with or without decreased GFR, with either pathological abnormalities or markers of kidney damage
- $\text{GFR} < 60 \text{ mL/min/1.73m}^2 > 3 \text{ months}$, with or without kidney damage

CKD is divided into stages:

- Stage 1 = normal GFR
- Stage 2 = GFR 60–89
- Stage 3 = GFR 30–59
- Stage 4 = GFR 15–29
- Stage 5 = GFR < 15 or on dialysis

These stages provide management guidelines for the expected complications of anemia, bone disease, hypertension, salt and water retention, and uremia. **Anemia**, from decreased erythropoietin, is **normochromic, normocytic**, and responds to **erythropoietin-stimulating agents**. Peripheral sensory **neuropathy** and “restless leg syndrome” may occur.

Patients with CKD have an increased risk of heart disease because of their underlying conditions—and because CKD, alone, is an independent risk factor—although we don’t know exactly all the factors involved. Heart disease is the number one cause of death.

BONE DISEASE IN CKD

As GFR declines, the kidneys become less able to excrete phosphorus in the urine. Serum phosphorous levels remain normal until ~ stage 3 CKD, after which phosphorus accumulates in the blood. Phosphorous retention:

- Stimulates release of parathyroid hormone
- Is further associated with hypocalcemia-induced PTH release via 2 mechanisms:
 - Calcium and phosphorus complex together and deposit in the vasculature and tissues.
 - Low GFR inhibits production of active (1,25) vitamin D.

Know that hyperphosphatemia is associated with an increased risk of death and heart disease, even in patients without CKD—but especially in those with stages 3–5 CKD.

As the phosphorous levels accumulate, our traditional strategy has been to prescribe **calcium-based** phosphate binders to prevent the development of secondary hyperparathyroidism and renal osteodystrophy. What we now know is that these calcium-based binders can actually cause the calcium levels to increase, and the resultant hypercalcemia then inhibits PTH release. This is not a good thing.

Bone needs to turn over some—not too much (as occurs with hyperparathyroidism), but not too little either (this situation is called “adynamic bone”). When we treat renal patients for their increasing phosphorous, we can interrupt the fine balance of required bone turnover. If we don’t treat their secondary hyperparathyroidism, the bone turns over too much; if we overtreat it, the bone turns over too little. Phosphate binders are either **calcium-based** (CaCO_3 or Ca acetate) or **noncalcium-based**, such as sevelamer (Renagel®) and lanthanum (Fosrenol®).

To summarize, the sequence of events goes like this for bone disease in CKD:

Decreased GFR (stage 3 CKD) → increased PO_4 , normal/low-normal Ca, increased intact PTH (iPTH) → secondary HPTH and vascular calcification.

The development of the noncalcium-based phosphate binders, along with regular measurement of iPTH levels, have greatly improved the management of mineral metabolism in CKD patients. Ideal management is to control phosphorus with diet and calcium-based phosphate binder, which will lead to normalization of phosphorous, increased Ca, and decreased iPTH. However, if the PTH is lowered all the way to the normal range, low bone turnover (adynamic bone) results.

So know that patients with CKD can have 3 types of bone disorders:

- 1) **Renal osteodystrophy** due to secondary hyperparathyroidism (high bone-turnover disorder)

Quick Quiz

- What is the definition of chronic kidney disease?
 - What is the effect of chronic hyperphosphatemia in patients with CKD?
 - What bone disorders are associated with CKD?
 - How is adynamic bone disease different from secondary hyperparathyroidism?
 - Which phosphate binders should be used in the hypercalcemic patient?
 - What are the signs/symptoms of uremia?
- 2) **Adynamic bone** disease due to suppression of parathyroid hormone release (low bone-turnover disorder)
 - 3) **Osteomalacia** (low bone-turnover disorder associated with unmineralized bone)

Renal Osteodystrophy

Review of secondary hyperparathyroidism: Labs = $\uparrow$ PO_4 , $\downarrow$ $1,25\text{-(OH)}_2\text{-D}$, $\uparrow$ $\uparrow$ iPTH , calcium normal/low-normal.

Treat this by following intact PTH (iPTH) levels and giving phosphate binders, 25-OH- and/or $1,25\text{-(OH)}_2\text{-D}$, or one of the available analogs (paricalcitol, doxercalciferol) +/- calcimimetics (cinacalcet). Calcimimetics are new drugs that increase parathyroid receptor sensitivity to calcium and reduce PTH.

Which phosphate binder to choose is based on the patient's serum calcium level. We used to treat to keep the calcium-phosphorous product below a specific number, but newer recommendations stress that the product is not as important as the iPTH level. The goal with treatment is to normalize phosphorus without creating adynamic bone.

Current recommendations for stages 3–5 CKD not on dialysis:

- Start with calcium-based binders when the iPTH level starts to increase above “normal,” if the serum calcium is 8.5–9.5 mg/dL.
- Monitor the serum calcium and iPTH. Change to a noncalcium-based binder if the serum calcium increases > 9.5 mg/dL or the iPTH is < 100 pg/dL.
- Give doses to target normal serum phosphorous and calcium levels.

Dialysis patients:

- Aim for an iPTH 2–9 x normal.
- Give doses to keep phosphorous 3.5–5.5 mg/dL and calcium 8.4–9.5 mg/dL.
- Make sure hypocalcemic patients are not vitamin D deficient.

Adynamic Bone Disease

Review of adynamic bone disease: Labs = $\uparrow$ /nl PO_4 , $\downarrow$ $1,25\text{-(OH)}_2\text{-D}$, $\downarrow$ iPTH , and calcium normal or high.

Adynamic bone disease is an important type of bone disease in CKD patients on dialysis. It is a low bone-turnover state accompanied by reduced bone formation. The cause is oversuppression of PTH by phosphorous binders and concomitant prescription of vitamin D analogs. Think of it as a sequela of overtreatment of CKD's secondary hyperparathyroidism. And for this reason, iPTH levels in CKD patients have to be closely followed so as not to undertreat or overtrear.

Most patients with adynamic bone disease are asymptomatic, but they can have fractures and hypercalcemia (especially if on analogs and calcium-based binders). Diagnose by observing an intact PTH level of < 100 pg/mL in a patient with CKD. Treatment requires reducing the amount of vitamin D analog and calcium-based phosphate binders (or substituting them with noncalcium-based binders).

Osteomalacia

Osteomalacia is uncommon in CKD now, and historically was due to the use of aluminum-containing phosphate binders that caused aluminum toxicity. Osteomalacia may still occur due to vitamin D deficiency.

UREMIA IN CKD

A strict definition of uremia doesn't exist because what we label as “uremia” changes as our understanding of chronic kidney disease evolves. Nevertheless, uremia is associated with a GFR < 15 cc/minute and a constellation of findings that depend on the severity of uremia and includes anorexia, nausea/vomiting, pericardial and pleural effusions, hemorrhagic pericarditis, platelet dysfunction and bleeding, hyperparathyroidism, pruritus, sensory neuropathies, central nervous system dysfunction, and an increased anion gap metabolic acidosis. (Uremia does not cause any liver dysfunction.)

ENDOCRINE PROBLEMS IN CKD

CKD also can cause decreased glucose tolerance, decreased gonadal hormone production (with impotence or amenorrhea/infertility), and a low T_3 with a normal TSH.

ANEMIA IN CKD

The **normochromic-normocytic anemia** in CKD responds dramatically to recombinant erythropoietin. The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative published recommendations (updated in 2007) for treatment of anemia in CKD using erythropoietin-stimulating agents (ESAs).

Before starting treatment with ESAs, ensure there are plenty of iron stores on board (Fe saturation is greater than 20% and ferritin levels are > 100 , and replenish with either oral or intravenous iron if stores are low).

While the 2007 guidelines for ESA treatment in CKD targeted a hemoglobin range of 11–12 g/dL, clinical trials that incorporate ESAs have shown **no improvement** in outcome and an **increased morbidity and mortality** if the hemoglobin is **normalized**. Now, nephrologists recommend that initiation of an ESA should be based on the clinical status of the patient and **not** on an absolute hemoglobin level.

TREATMENT OF CKD

Progression of CKD is slowed by **ACEIs or ARBs** (target BP = $< 130/80$) and possibly by reduced protein intake (controversial). ACEIs and ARBs decrease intraglomerular pressure, which decreases progression. Recent data suggest that angiotensin II turns on TNF- β , which stimulates fibrosis, and this also may be suppressed by ACEIs/ARBs.

Aggressive management of comorbidities may also decrease progression, so treat metabolic acidosis and hyperlipidemia and counsel to stop smoking. As the disease worsens, **avoid nephrotoxins**—especially contrast dye, NSAIDs, and aminoglycosides.

GOUT IN CKD

Gout can occur in CKD. An exacerbation can still be treated with colchicine or NSAIDs, although you must strictly monitor kidney function. Allopurinol decreases the production of uric acid, and chronic usage is often necessary. (Probenecid works by increasing renal excretion of uric acid. It is not effective and **contraindicated** in CKD.) For gout affecting a single joint, an intraarticular steroid injection is the preferred treatment.

DIALYSIS

Dialysis—When to start? Answer: When the CKD patient has **advancing uremia**. This usually means **any** uremic symptoms in a patient with a CrCl < 15 mL/min. Starting at a specific BUN or creatinine value is of **no** proven benefit. A forearm AV fistula lasts the longest but should be created several months before dialysis; otherwise, a prosthetic graft is needed. Refer patients when they develop Stage IV CKD (GFR < 30 mL/min/1.73m²).

Know that the most common cause of **death** in dialysis patients is **cardiovascular** disease. Next is infection. The most common cause of admission is thrombosis/infection of the vascular access.

Dialysis patients have anemia, high triglycerides, and a low HDL. They usually have a metabolic acidosis just before and a respiratory alkalosis just after dialysis.

Maintaining **adequate nutrition** in these patients is one of the key factors in reducing morbidity and mortality. Vitamin supplements are indicated, especially water-soluble and folate. Water-soluble vitamins are vitamins that are not stored in fat; they must be replenished each day. The main water-soluble vitamins are B-complex and vitamin C.

Continuous Ambulatory Peritoneal Dialysis (CAPD). With CAPD, you do **not** need an AV fistula or sophisticated machinery, but pay close attention to nutritional status—a high-protein intake is necessary. Fluid shifts are more gradual so CAPD causes less strain on the heart.

The patient infuses 2–3 L of hypertonic dextrose solution into the peritoneal cavity (subsequently drained by gravity) 4–6 times per day.

For CAPD, the main complication is **peritonitis**, usually caused by gram-positive skin flora (usually *S. epidermidis* or *S. aureus*), and next most commonly, gram-negative organisms. Empiric intraperitoneal therapy with agents effective against these organisms should be initiated in suspected peritonitis while cultures are pending. Peritonitis should be suspected when the cell count of peritoneal fluid shows > 100 cells with $> 50\%$ PMN's. Other CAPD problems include hernias, hydrothorax, high protein loss (12 g/d) and loss of water-soluble vitamins (especially folic acid).

Decreased renal function increases the half-lives of many drugs, which may actually facilitate administration.

DRUG METABOLISM IN CKD

Vancomycin is completely excreted by the kidney; therefore, dosing intervals are markedly prolonged (dose required only once every few days and titrated based on serum levels of vancomycin). On the other hand, **amino-glycosides** can be completely removed during dialysis, and therefore need to be re-dosed after treatment.

Drugs that require dosing reductions. Some drugs that require dosing reductions as renal functions deteriorates are:

- digoxin,
- glyburide,
- procainamide, and
- gabapentin.

Need to re-dose after dialysis. Many antibiotics have some clearance during dialysis; therefore, they should be re-dosed after the session and may require supplemental doses. The common ones include:

- most beta-lactams,
- daptomycin,
- metronidazole,
- ciprofloxacin, and
- levofloxacin.

Quick Quiz

- How is normochromic-normocytic anemia in CKD treated? What is the target hemoglobin (read all 3 paragraphs!)?
- When is dialysis initiated in a CKD patient?
- What is the most common cause of death in the dialysis patient?
- What organisms are associated with peritonitis in the patient on CAPD?
- What is the risk of gadolinium use in the patient with CKD?
- Which immunomodulators are used in renal transplant patients?

IMAGING IN CKD

Avoid gadolinium contrast in patients with **CKD**.

Know that **gadolinium**, a contrast material used in MRIs, is associated with **nephrogenic systemic fibrosis** (NSF) in patients with advanced CKD (all forms, regardless of whether on dialysis or what type of dialysis). Some data suggest that NSF is gadolinium dose-dependent and that it may also be associated with erythropoietin use.

Disease presents as a thickening of the skin with symmetric plaques, papules, or nodules. Skin may have redness and induration. Usually it **starts distally** and moves to proximal skin. Sometimes systemic symptoms are associated: organ fibrosis, scleral yellowing, and tissue calcification.

Presentation may be concerning for development of an autoimmune disease. Know that sclerodactyly can occur, but livedo reticularis is not associated with NSF. Definitive diagnosis is made with deep punch biopsies of involved skin. Lab tests generally focus on excluding autoimmune disease. NSF is not associated with eosinophilia, abnormal thyroid function tests, CPK elevation, antinuclear antibodies, antiphospholipid antibodies, or rheumatoid factor.

Course is progressive, sometimes fulminant. If renal recovery occurs, usually the NSF will remit—otherwise, there is no treatment.

RENAL TRANSPLANT

Anytime renal function deteriorates in a patient with a kidney transplant, think in the usual terms: Is it prerenal, postrenal, or intrinsic renal? Delayed graft function due to ischemia ATN is the most common cause of intrinsic renal disease immediately post-transplant. Immediate failure of the transplant (called “hyperacute rejection”) can also be due to preformed donor antibodies that acutely cause damage to the kidney, even at surgical implantation (kidney becomes discolored and mottled). In almost all transplant centers, early renal dysfunction is evaluated by renal biopsy.

If the kidney functioned well after transplant but deteriorates **within the first 3 months**, again consider whether the problem is prerenal, postrenal, or intrinsic renal. Intrinsic renal causes are the most problematic and include rejection, drug-induced toxicity, infection (CMV or BK virus), and recurrence of disease for which the kidney was transplanted.

Unless evidence is overwhelming for intrinsic renal causes (e.g., return of active urine sediment), start workup by checking levels of **immunosuppressant** drugs: **cyclosporine**, **tacrolimus**, **sirolimus**. Screen for CMV and BK virus and obtain renal ultrasound. If these are normal or the patient’s renal function is not improving, renal biopsy is indicated.

Cyclosporine and **tacrolimus** are calcineurin inhibitors (CNI) with similar mechanisms of action. They decrease T-cell proliferation (but **not** function!) **without** affecting the bone marrow. **Sirolimus** is an mTOR kinase inhibitor currently used at some institutions, also with antiproliferative properties. It is always used with cyclosporine initially. All 3 drugs cause dose-related nephrotoxicity and carry FDA-boxed warnings for increased risk of death from infections. Side effects of cyclosporine include tremors, hepato/CNS toxicity, and gum hypertrophy. Tacrolimus is more diabetogenic. Sirolimus is associated with wound dehiscence/impaired healing, and development of lymphoma and hyperlipidemia. All are metabolized by the cytochrome P-450 system. **Blood levels are increased** by erythromycin, ketoconazole, voriconazole, and diltiazem—and **decreased** by phenytoin, caspofungin, carbamazepine, rifampin, and phenobarbital.

Mycophenolate mofetil is routinely used in most centers and has largely replaced a similar, older agent, **azathioprine**. Its main side effects are GI with some BM suppression, and it may increase risk for lymphoproliferative disorders. Know that allopurinol increases serum levels of azathioprine but not MMF.

Immunosuppression: Most patients are on “triple therapy” with CNI (or sirolimus), MMF, and a corticosteroid, although many variations of treatment exist.

Urinary tract infections, pneumonia, and sepsis are common events after renal transplant. Patients are given primary prophylaxis against *Pneumocystis* for 1 year post-transplant and against CMV for 3 months. Renal transplant patients are also more likely to get post-transfusion hepatitis, aseptic necrosis of femoral heads, and cataracts. Primary renal disease can recur with FGS, MPGN, IgA nephropathy, and even diabetes. The main cause of death after kidney transplant is **cardiovascular disease**.

Both dialysis and renal transplant reverse the platelet dysfunction, renal osteodystrophy, and sensory/cognitive dysfunction of CKD. Only transplant can reverse late manifestations of small vessel calcification and motor neuropathy in CKD.

HEREDITARY KIDNEY DISEASES

ALPORT'S

Alport syndrome = hereditary nephritis (also discussed under normal complement nephritic syndromes on (page 4-36). Alport syndrome can be either **X-linked** (typical case) or **autosomal dominant** (AD) with variable expression. Men are affected more seriously than women.

Alport syndrome results from a type IV collagen connective tissue defect that affects the **basement membrane** (the same target as the Goodpasture's anti-GBM antigens!), cochlea, and the lens. Hearing loss is common. The female X-linked carriers have microscopic hematuria only. The affected males usually have renal failure by the time they are adults.

Consider Alport syndrome in any patient with persistent microscopic hematuria (onset at birth) that worsens after an infection (i.e., include this in the differential diagnosis of PIGN and IgA nephropathy). Also, especially consider Alport syndrome in a woman with microscopic hematuria when there is a family history of males dying of kidney problems. Diagnose with a kidney biopsy in both men and women. Thinning of the basement membrane occurs in both Alport syndrome and the related though benign condition, "thin basement membrane" disease, which can present with asymptomatic intermittent hematuria.

Disease is treated with an ACEI or ARB, because no other therapy has proven effective in a randomized controlled trial. Renal failure is treated with transplantation.

POLYCYSTIC KIDNEY

Autosomal dominant polycystic kidney disease (PCKD) is the most common genetic disease of the kidney. It is usually associated with a mutation on the short arm of chromosome 16. There is a locus near the defective gene that, when found, suggests a tendency for the disease.

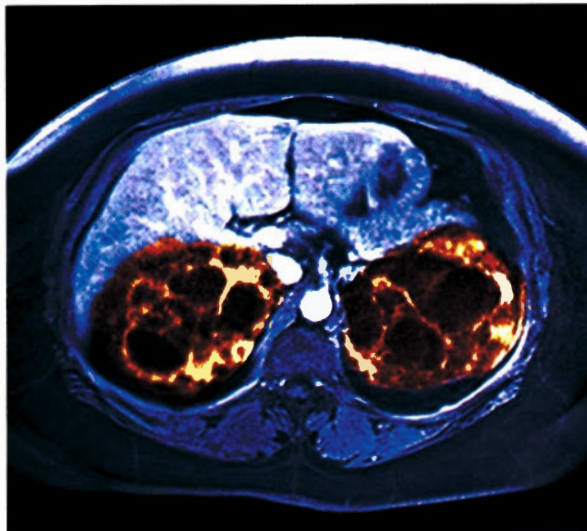


Image 4-7: Polycystic kidneys on MRI

Patients get cysts of the kidneys, liver, and pancreas as well as associated recurrent hematuria (Image 4-7).

Onset of polycystic kidney disease occurs at ~ age 20. Gross or microscopic hematuria is the most common presenting symptom. Patients also can present with flank pain, chronic kidney disease, hypertension, and cyst infections. Progressive renal failure and HTN are the norm. Associated liver cysts cause hepatomegaly but **rarely** liver dysfunction. Cerebral aneurysms occur in a very small percent (1–5%).

Screening for aneurysms is recommended if the patient with PCKD has 1 or more relatives with a history of subarachnoid hemorrhage or a known aneurysm. Some experts also recommend that a patient with PCKD be screened if she has an occupation that places her own life or the lives of others at risk should she lose consciousness.

The diagnosis is usually established when polycystic kidneys are identified by imaging (U/S or CT) during evaluation for hematuria. Renal U/S is also used for screening patients > 18 years of age with a family history of PCKD. Genetic testing is available when the diagnosis is in question.

MEDULLARY DISEASE

There are 2 main inherited medullary kidney diseases:

- 1) **Medullary sponge disease** (diagnosed by IVP), which is rarely clinically significant but is associated with high PTH, hypercalciuria, and renal stone disease.
- 2) **Medullary cystic disease**, which can cause renal failure and presents in childhood. This is one of the few chronic kidney diseases in which there usually is a **normal** urinalysis.

HEMATURIA

The big challenge is determining if hematuria is due to intrinsic renal disease or genitourinary bleeding. **Hematuria** associated with **proteinuria**, especially if **RBC casts** are present in the urine, **is always** due to glomerular bleeding. Isolated microscopic or gross hematuria is more likely to be urologic in origin. In older patients, complete GU imaging with renal U/S, MRI, or CT must be performed to exclude renal cell or other GU tract carcinomas.

RENAL CYSTS

Renal cysts are very common: 50% of people > 50 years old have them. They are considered benign if "simple" on U/S and the patient is asymptomatic. "Simple" cysts have well-defined margins, dense (compressed) surrounding tissues, and no echoes. Otherwise, cyst

Quick Quiz

- What are the presenting symptoms of polycystic kidney disease?
- What lab findings suggest that hematuria is caused by GN?
- When is a renal cyst considered benign?
- Which antiretroviral drug is associated with renal stones?
- Name the common causes of calcium stones.
- Which bacteria are associated with staghorn calculi?
- Name one of the most important general recommendations for patients with kidney stones, regardless of the type of stones.

aspiration or surgical exploration is indicated to rule out cancer. Also see polycystic kidney disease above.

RENAL STONES

Renal stones: 2/3 of renal stones are either **calcium** phosphate or calcium oxalate; the other 1/3 are **struvite** or **uric acid**. Struvite is a phosphate stone with a mixture of cations: calcium/ammonium/magnesium phosphate (Image 4-8 and Image 4-9). Don't forget that patients with HIV/AIDS on indinavir as part of an antiretroviral regimen can get indinavir stones.

Workup following **initial** stone passage usually includes:

- Chemical analysis of the stone
- Calcium level (Exclude **hyper**parathyroidism.)
- Electrolytes and urine pH (Exclude Type 1 distal RTA.)
- U/A with C+S (Exclude stone-forming urinary pathogens.)

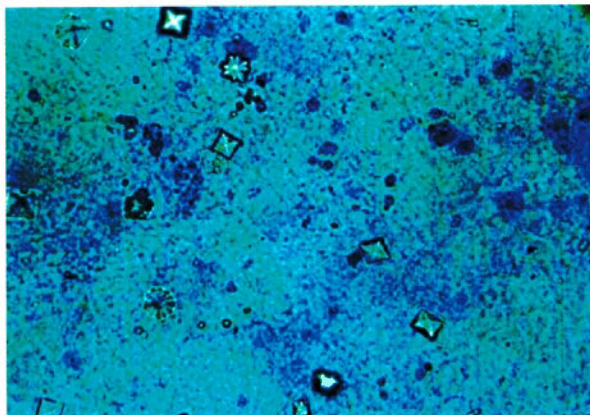


Image 4-8: Calcium oxalate crystals (squares) in urine

- Renal imaging (Helical CT is the imaging of choice; rarely use IVP. In patients with impaired renal function, begin with ultrasound imaging of the kidney.)

When it is a **first** stone in a low-risk patient (no illnesses and negative family history) **and** the stone is **not** retrieved, limited evaluation is appropriate: serum chemistry including calcium. If serum calcium is elevated x2, work up for primary hyperparathyroidism. All these patients are told to push fluids enough to produce **2 L/d** of urine.

For **recurrent** stones, check urine for the following: volume, cystine, calcium, Na, urea, uric acid, citrate, oxalate, and creatinine. If there are signs of acute ureteral obstruction with infection, the patient **must** be hospitalized because sepsis and papillary necrosis may result.

There are several factors that **inhibit** or **promote** stone formation. **Citrate** is the major inhibitor of calcium stones, but magnesium and pyrophosphate are also inhibitors. Concentrated urine and/or excretion of excessive amounts of stone-forming products cause precipitation and stone formation. Finally, certain products may act as a nidus for stone formation.

Calcium stone causes: hypercalciuria, uric acid, hypocitraturia, hyperoxaluria, and medullary sponge disease. Citrate chelates calcium, thereby preventing stones. Acidosis causes hypocitraturia and also leaches calcium from the bones, resulting in hypercalciuria. Although the calcium stones are usually a combination, they are often grouped into **calcium phosphate** and **calcium oxalate** stones.

Hypercalciuria can be caused by hypervitaminosis D, distal (Type 1) RTA, sarcoidosis, and hyperparathyroidism. 1/2 of the patients have "idiopathic" hypercalciuria, now known to be caused by increased calcium absorption from the gut, secondary to an increased renal production of 1,25-(OH)₂-D.

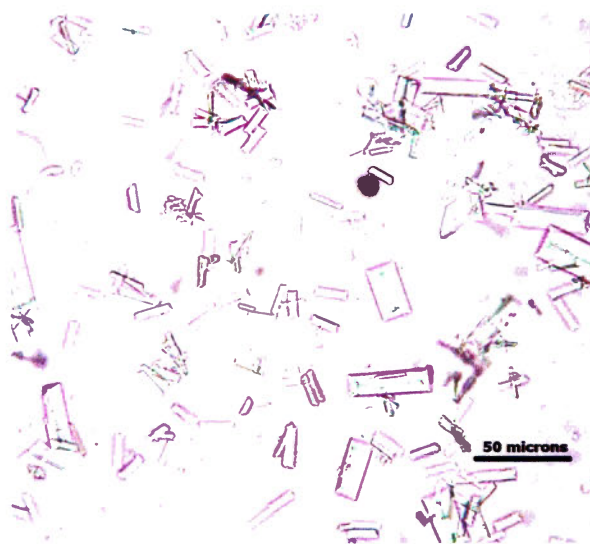


Image 4-9: Struvite crystals (coffin lids)

Calcium phosphate stones are more common in patients with 1° hyperparathyroidism, acetazolamide, and distal (Type 1) RTA. Distal RTA causes stones by 1) causing an increase in CaPO_4 withdrawal from bones (remember that phosphorus is one of the body's main acid buffers!), and 2) producing an alkaline urine that allows this increased CaPO_4 to precipitate.

High urinary **oxalate** is the most important factor in calcium oxalate stone formation. **Vitamin C** and **ethylene glycol** are oxalate precursors and, theoretically, can cause stones if taken in large amounts. (Ethylene glycol will kill you first!) **Steatorrhea** also causes oxaluria; free fatty acids in the bowel chelate the calcium, allowing the oxalate to be absorbed and then excreted in the urine. Uricosuria is a predisposing factor for oxalate stones because the **uric acid crystal** is similar to calcium oxalate and can act as a nidus for stone formation.

Treat calcium stones by pushing fluids, giving thiazide diuretics for hypercalciuria (decrease urinary calcium), decreasing dietary protein and sodium, giving potassium citrate, and treating high uric acid. Note: Do **not** decrease calcium intake; this only **increases** oxaluria!

Struvite (calcium/ammonium/magnesium phosphate) stones grow quickly and often cause **staghorn calculi**. Think **infection** when you see staghorn calculi. The **ammonium** needed to make these stones forms only when **urease** breaks down the urea. The most common urease producers are *Proteus* and *Klebsiella*. Treatment consists of removal of the stones/calculi; acidification of the urine (this is the only other stone, besides calcium phosphate, made **more likely** by alkaline urine); and antibiotics. If all of the stones cannot be surgically removed, patients require indefinite antibiotics.

Cystine stones are due to cystinuria. Cystine is undersaturated in the normal urine, but homozygous patients with cystinuria excrete large amounts (autosomal recessive genetics). Look for clear, **hexagonal** crystals in the urine. Cystine is **insoluble**. It is usually best to treat by increasing **fluids** and by **alkalinizing** the urine—to keep urine cystine concentration normal! Penicillamine forms soluble complexes with cystine but is not well tolerated. Heterozygotes do not form stones.

Uric acid stones are usually seen in patients who chronically excrete acidic urine. You also see them in those who have high serum uric acid. Myeloproliferative syndromes, chemotherapy, and Lesch-Nyhan syndrome can cause such hyperuricosuria in which there is stone formation even at normal urine pH. Treat with allopurinol +/- urinary alkalinization. Give allopurinol before treatment of high cellular tumors. Avoid urinary alkalinization if there is also hypercalciuria.

Treatment options for acute ureteral obstruction include:

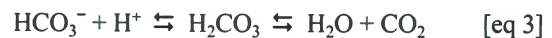
- Allow passage (if less than 0.5 mm).
- Remove via ureterorenoscopy (middle and distal stones).

- Remove via percutaneous nephrostolithotomy (staghorn and other large stones).
- Remove via percutaneous ultrasonic lithotripsy (continues to be associated with high complication rate).

Know that urinary **alkalinization** is done for all stone-formers, **except** in struvite and calcium phosphate stones. And push fluids so the patient produces about **2 L/day** of urine, regardless of the type of stones. Also remember the difference between cystine and citrate: **Cystine** is an amino acid that precipitates into stones, while **citrate** chelates calcium in the urine, thereby preventing stones.

APPENDIX A

You hear a lot about the Henderson-Hasselbalch equation. Did you know that it is derived from the bicarbonate buffer equation:



H_2CO_3 is carbonic acid. HCO_3^- is bicarbonate. CO_2 is carbon dioxide. In the serum, these 3 molecules exist in equilibrium with one another.

From the law of mass action is derived the dissociation constant for carbonic acid K_{Ai} :

$K_{\text{Ai}} = (\text{H}^+ \times \text{HCO}_3^-) / \text{H}_2\text{CO}_3$; and since CO_2 is in equilibrium with H_2CO_3 , an equilibrium constant is added to K_{Ai} , and we get:

$$K_{\text{A}} = (\text{H}^+ \times \text{HCO}_3^-) / \text{CO}_2 = \text{H}^+ \times (\text{HCO}_3^- / \text{CO}_2)$$

Taking logarithms:

$$\log K_{\text{A}} = \log \text{H}^+ + \log (\text{HCO}_3^- / \text{CO}_2)$$

so:

$$-\log \text{H}^+ = -\log K_{\text{A}} + \log (\text{HCO}_3^- / \text{CO}_2)$$

Noting that dissolved CO_2 is a function of the partial pressure of CO_2 in blood, $\text{CO}_2 = 0.03 P_{\text{aCO}_2}$; and that $\text{pH} = \log [1/\text{H}^+] = -\log [\text{H}^+]$, we get the Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK} + \log (\text{HCO}_3^- / [0.03 \times P_{\text{aCO}_2}]) \quad [\text{eq 4}]$$

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